

Impact of Pramlintide on Glucose Fluctuations and Postprandial Glucose, Glucagon, and Triglyceride Excursions Among Patients With Type 1 Diabetes Intensively Treated With Insulin Pumps

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OBJECTIVE — To assess the effects of adjunctive treatment with pramlintide, an analog of the β -cell hormone amylin, on 24-h glucose fluctuations and postprandial glucose, glucagon, and triglyceride excursions in patients with type 1 diabetes intensively treated with continuous subcutaneous insulin infusion (CSII).

RESEARCH DESIGN AND METHODS — In this study, 18 patients (16 of whom could be evaluated) with type 1 diabetes (age 44 ± 11 years, HbA_{1c} $8.2 \pm 1.3\%$ [mean \pm SD]) were given mealtime injections of 30 μ g pramlintide t.i.d. for 4 weeks in addition to their preexisting CSII regimen (16 lispro, 2 regular insulin). Mealtime insulin boluses were reduced by a minimum of 10% during the first 3 days, and re-adjusted thereafter based on clinical judgment. At weeks 0 (baseline), 4 (on treatment), and 6 (2 weeks off treatment), 24-h interstitial glucose concentrations were measured using a continuous glucose monitoring system (CGMS), and postprandial plasma glucose, glucagon, and triglyceride concentrations were measured in response to a standardized test meal.

RESULTS — At baseline, patients had excessive 24-h glucose fluctuations, with 59% of the CGMS measurements >140 mg/dl, 13% <80 mg/dl, and only 28% in the euglycemic range (80–140 mg/dl). After 4 weeks on pramlintide, measurements in the hyperglycemic range declined to 48% and measurements within the euglycemic range increased to 37%. This shift from the hyperglycemic to the euglycemic range occurred with a concomitant 17% reduction in mealtime insulin dosages and without relevant increases in measurements below the euglycemic range (15%) or any severe hypoglycemic events. After 4 weeks on pramlintide, postprandial glucose, glucagon, and triglyceride excursions were reduced by ~ 86 , ~ 87 , and $\sim 72\%$, respectively (incremental areas under the curve, all $P < 0.05$ vs. baseline). At week 6 (off treatment), the 24-h glucose profile and postprandial glucose, glucagon, and triglyceride excursions approached pretreatment values.

CONCLUSIONS — In this study, the addition of pramlintide to insulin therapy reduced excessive 24-h glucose fluctuations as well as postprandial glucose, glucagon, and triglyceride excursions in patients with type 1 diabetes intensively treated with insulin pumps.

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Abbreviations: AUC, area under the curve; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion; TSH, thyroid-stimulating hormone.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Despite important advances in the delivery and pharmacology of insulin, such as the development of continuous subcutaneous insulin infusion (CSII) and rapid- and long-acting insulin analogs, many patients with type 1 diabetes still fail to achieve glycemic targets (1). An important barrier to achieving tight glycemic control with insulin therapy alone is that patients with type 1 diabetes, even when on intensive insulin regimens, frequently experience excessive glucose fluctuations throughout the day, most notably in the postprandial period, compared to the narrow glycemic range seen in nondiabetic individuals (2–7). The magnitude of this problem has only recently begun to be recognized with the clinical application of glucose sensor technology that, unlike the finger-stick method, allows continuous monitoring of glucose concentrations throughout the day (2,4–7). Using this technology, several investigators have demonstrated an unexpectedly high prevalence of excessive postprandial hyperglycemic excursions and unrecognized nocturnal hypoglycemic episodes in adolescents and adult patients with type 1 diabetes (2,5). It has been suggested that these excessive glucose peaks may convey an increased risk of micro- and perhaps macrovascular complications independent of HbA_{1c} (8). From the patient's perspective, excessive and unpredictable glucose fluctuations are often perceived as a cause of frustration and a major barrier to achieving glycemic targets (6,9).

Amylin is a second glucoregulatory β -cell hormone that is normally co-secreted with insulin in response to meals, and, like insulin, is absolutely deficient in patients with type 1 diabetes (10–14). Preclinical studies have indicated that amylin acts as a neuroendocrine hormone that complements the actions of insulin in postprandial glucose

control via several mechanisms (10–14). These mechanisms include a suppression of nutrient-stimulated glucagon secretion (15) and a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption (16), thereby reducing the influx of glucose into the circulation to a rate that better matches the rate of insulin-mediated glucose efflux.

Pramlintide is a synthetic analog of human amylin under development as an adjunct to insulin therapy in both type 1 and type 2 diabetes (10–12,14). Clinical studies in patients with type 1 diabetes have shown that mealtime amylin replacement via subcutaneous injections of pramlintide, as an adjunct to insulin therapy, suppresses mealtime glucagon secretion (17,18), slows the rate of gastric emptying (19), and, consequently, improves postprandial glucose excursions (18,20). Long-term clinical studies in patients with type 1 diabetes have shown that the addition of pramlintide to existing insulin therapy leads to a significant and sustained reduction in HbA_{1c}. These reductions are accompanied by weight loss rather than weight gain and occur without an overall long-term increase in the event rate of severe hypoglycemia (21–23).

The aim of this study was to assess the effect of pramlintide on 24-h glucose fluctuations and postprandial plasma glucose, glucagon, and triglyceride excursions in patients with type 1 diabetes intensively treated with CSII.

RESEARCH DESIGN AND METHODS

Subjects

The patients enrolled in this study had type 1 diabetes for ≥ 1 year, and most had been intensively treated using a CSII basal/bolus regimen for at least 6 months. Patients were using either lispro or regular insulin, had not changed their total daily insulin dosage by more than $\pm 10\%$ for 2 months before the study, and had been free from severe hyper- and hypoglycemic symptoms for at least 4 weeks before the study. Exclusion criteria included a clinically significant history or presence of cardiac disease; untreated or poorly controlled hypertension (blood pressure $\geq 160/90$ mmHg); gastrointestinal, hepatic, renal, or central nervous sys-

tem disorders; acute illness; a history of drug or alcohol abuse; or treatment with drugs known to affect gastrointestinal motility or glucose metabolism.

A total of 24 subjects were enrolled. Using a 3:1 block randomization, 18 subjects were assigned to pramlintide and 6 were assigned to placebo treatment. The small placebo group was included to allow a blinding to therapy for patients and to provide data that could be used to conduct adequate power calculations when planning future studies with the continuous glucose monitoring system (CGMS). Because the study was not powered for the purpose of statistical pramlintide versus placebo comparisons, CGMS data from the placebo group are presented as a point of reference only. As an internal control for the pramlintide treatment group, a third assessment was performed 2 weeks after termination of pramlintide.

One subject withdrew from the study because of an adverse event. Another subject was retrospectively excluded because of a markedly increased screening thyroid-stimulating hormone (TSH) level that violated the inclusion/exclusion criteria (the subject had been erroneously enrolled even though his TSH level did not meet those criteria). The study protocol was approved by the respective Institutional Review Boards of the two study centers and all patients provided written informed consent.

Design

The study consisted of three time periods: baseline, 4 weeks of treatment, and 2 weeks after treatment. At the end of each time period (weeks 0, 4, and 6), patients underwent a standardized meal test and a 3-day sensor measurement using a CGMS (MiniMed; Medtronic, Northridge, CA).

The baseline assessments (week 0) were conducted with patients being treated solely with their usual CSII regimen. After the baseline assessments, patients were instructed to self-administer injections of pramlintide or placebo t.i.d. with their major meals, in addition to their existing CSII therapy, for 4 weeks. Study medication was self-administered within 15 min of major meals and was injected subcutaneously into the anterior abdominal wall, opposite the insertion site of the CSII catheter. To minimize the risk of hypoglycemia after initiation of pramlintide treatment, all patients were instructed to reduce their mealtime insu-

lin dosages by a minimum of 10% during the first 3 days of treatment and to subsequently titrate their insulin dosage as clinically indicated based on blood glucose self-monitoring results. Patients recorded their daily insulin regimen in diaries throughout the study. The insulin dosage regimen and blood glucose self-monitoring results were reviewed by the investigator at each visit, and insulin regimens were adjusted as appropriate. Then 3 days before the end of the 4-week on-treatment period, patients repeated the 3-day CGMS measurement and the standardized meal test while still receiving study medication. Patients then resumed their preexisting therapy (CSII only) and, after 2 weeks, had a third 3-day CGMS measurement and standardized meal test (week 6).

CGMS measurements

At each of the three evaluations, patients arrived at the office the morning after an overnight fast and the catheter of the CGMS device was inserted into the subcutaneous tissue of the anterior abdominal wall. The CGMS technique has been previously described in detail (2,5). In brief, interstitial glucose concentrations, which are known to correlate closely with blood/plasma concentrations, were assessed continuously every 5 min for 3 days, totaling 288 measurements during a 24-h period. Once the CGMS monitors were in place and calibrated and the standardized meal tests were completed, patients were discharged with instructions to resume their normal activities.

After 3 days, patients returned to the office for sensor removal and data download. To ensure data quality, all sensor readings were immediately evaluated by an independent reviewer who was blinded to the patients' treatment assignment. In the case of clear sensor failure, the patient was asked to return for a repeat assessment. From the 3-day measurement period, day 2 was prospectively chosen as the default 24-h period for data analysis. Day 3 data were assessed if the sensor readings from day 2 did not meet these prespecified data quality criteria: 1) ≥ 200 of 288 data points were collected, 2) there were no results during any consecutive 2-h period where sensor measurements were ≤ 40 mg/dl and self-monitored measurements for the same time period were >70 mg/dl, 3) there were no results during any consecutive

Table 1—Demographics and baseline characteristics of pramlintide-treated subjects

Sex (M/F)	8/10
Race (caucasian/other)	14/4
Age (years)	44 ± 11
Weight (kg)	78.0 ± 18.2
BMI (kg/m ²)	28.0 ± 5.0
Diabetes duration (years)	25 ± 10
HbA _{1c} (%)	8.2 ± 1.3
Serum fructosamine (μmol/l)	339 ± 64
Mealtime insulin bolus (units)	7 ± 5
Insulin type lispro/regular	16/2
Fasting plasma glucose (mg/dl)*	169 ± 15
Fasting plasma glucagon (pg/ml)	65 ± 5
Fasting plasma triglycerides (mg/dl)	81 ± 9

Data are means ± SD. * Conversion to SI units: value × 0.055.

2-h period where sensor measurements were ≥400 mg/dl and self-monitored measurements for the same time period were <200 mg/dl, and 4) the correlation coefficient between sensor data and finger-stick meter measurements on day 2 is not 0.25 less than the correlation coefficient on day 3.

Standardized meal test

Once the CGMS was in place, patients consumed a standardized mixed meal consisting of one bagel, one cheese slice, margarine, orange juice, and 2% milk (~20% of total daily caloric requirements; 55, 15, and 30% of calories derived from carbohydrate, protein, and fat, respectively), which was completely ingested within 15 min ($t = 0$ min). Patients received a subcutaneous injection of study medication with the meal and self-administered their insulin bolus immediately before the meal. Blood samples were collected at -30, -15, 30, 60, 90, 120, 150, and 180 min for determination of plasma glucose, glucagon, and triglyceride concentrations, measured by commercially available assays (Roche Diagnostics; Mannheim, Germany; Esoterix, Calabasas Hills, CA).

Statistical analyses

The primary goal of the study was to assess changes in 24-h glucose fluctuations and postprandial plasma glucose, glucagon, and triglyceride responses over time as a result of pramlintide treatment.

Main outcome variables included changes over time (weeks 0, 4, and 6) in 24-h glucose profiles as measured by CGMS, as well as in the incremental areas under the curve (AUCs), calculated by the

trapezoidal rule, for postprandial plasma glucose, glucagon, and triglyceride excursions. Other outcome variables included changes over time in insulin usage and serum fructosamine concentrations. Descriptive statistics were used for CGMS measurements, whereas analytical statistics were applied to mealtime parameters, (postprandial glucose, glucagon, and triglyceride concentrations). Statistical calculations for differences in AUCs were based on nonoverlapping 95% confidence intervals.

Safety evaluations were based on reports of adverse events in response to nondirected questioning, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs (blood pressure and pulse rate), electrocardiograms, and physical examinations in all patients.

RESULTS

Demographics and baseline characteristics are shown in Table 1

Insulin use

At the end of the 4-week pramlintide treatment, the mean mealtime insulin dosage, averaged over the three major meals of the day, was reduced by 17% (from 7.2 ± 5.2 to 6.0 ± 3.7 units at weeks 0 and 4, respectively). Two weeks after pramlintide treatment, patients had increased their mealtime insulin bolus to a level commensurate with baseline (7.4 ± 5.0 units at week 6).

Glucose profiles

Results of the CGMS measurements at weeks 0, 4, and 6 are illustrated in Figs. 1 and 2. During the baseline period (week

0), patients had excessive 24-h glucose fluctuations, with 59% of the measurements (~14.2 h) >140 mg/dl, 13% of the measurements (~3.0 h) <80 mg/dl, and 28% of the measurements (~7.0 h) within the euglycemic target range (80–140 mg/dl) (Fig. 1A). After 4 weeks of pramlintide treatment, measurements within the hyperglycemic range had decreased to 48% (~11.5 h), whereas measurements within the euglycemic target range had increased to 37% (~8.9 h) (Fig. 1B). Measurements below the euglycemic range remained largely unchanged (15%; ~3.6 h) (Fig. 1B). At week 6 (2 weeks after the pramlintide treatment period), the distribution of the 24-h glucose readings had reverted to near baseline (week 0) values (Fig. 1C).

After 4 weeks of pramlintide treatment, patients spent 38% less time with glucose readings >300 mg/dl and 29% less time with glucose readings >200 mg/dl (1.2 vs. 1.9 h and 5.2 vs. 7.3 h, respectively, compared to week 0). An example of a CGMS reading showing reduced glucose fluctuations after 4 weeks on pramlintide is shown in Fig. 2A.

As is shown in Fig. 2B and C, stratification of the 24-h sensor period into daytime (6:00 A.M. to 10:00 P.M.) and nighttime (10:00 P.M. to 6:00 A.M.) revealed that the pramlintide-induced shift in glucose readings from the hyperglycemic to the euglycemic range was most pronounced during the daytime period, although a similar but less pronounced shift was also observed during the night time period.

In the small placebo group, no consistent changes in the distribution of glucose readings were observed among weeks 0, 4, or 6 (hyperglycemic range 49 vs. 53 vs. 45%; euglycemic range 24 vs. 28 vs. 29%; hypoglycemic range 26 vs. 19 vs. 26, respectively).

After 4 weeks of pramlintide treatment, the mean 24-h glucose concentration had decreased from 168 mg/dl (week 0) to 151 mg/dl, and then reverted to 162 mg/dl (week 6).

Using the acceptance criteria developed for the study, 97% of the sensor data came from day 2 measurements and 3% came from day 3 measurements. Repeat monitoring was required for 17% of the placebo-treated patients and 19% of the pramlintide-treated patients.

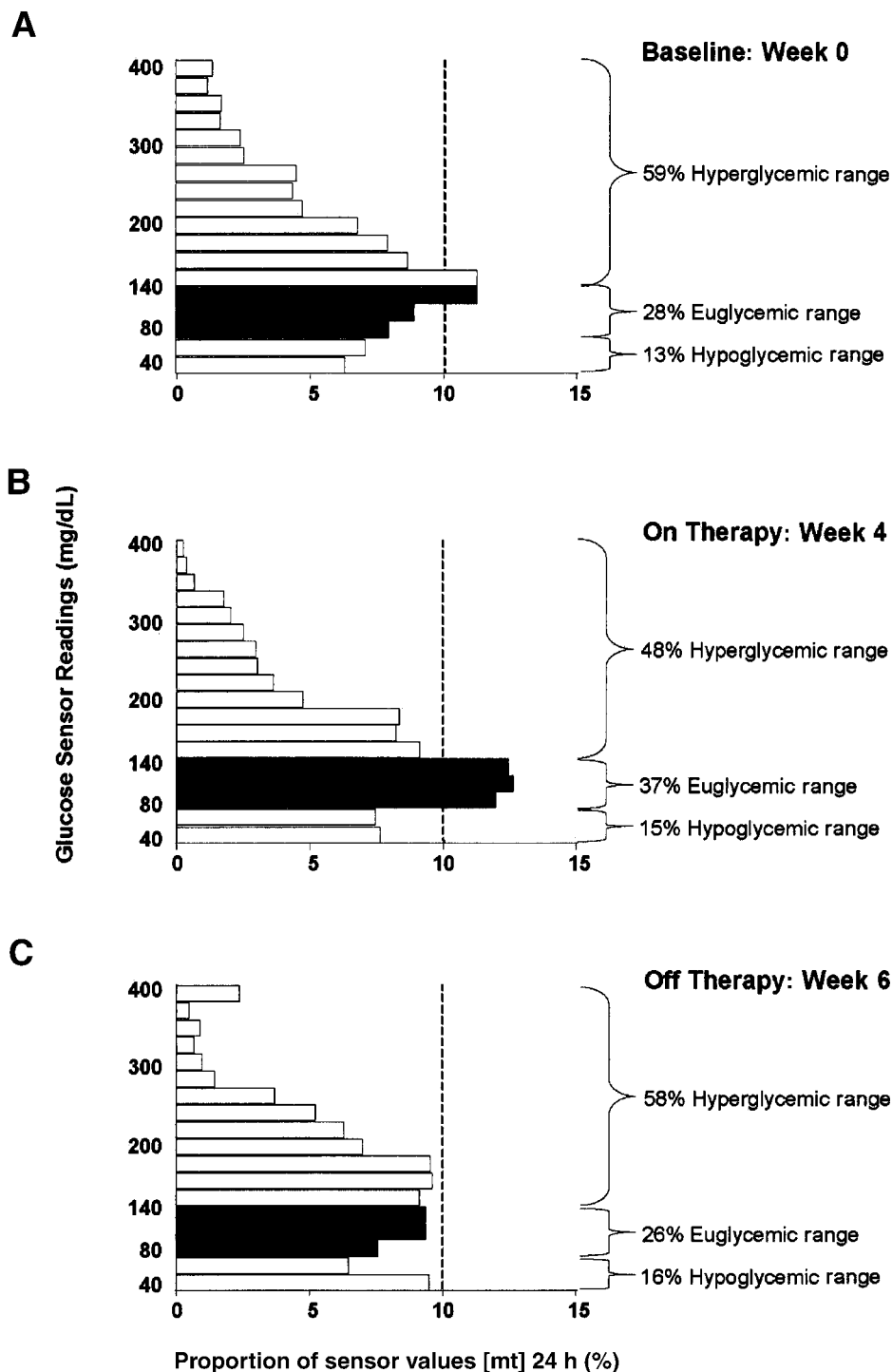


Figure 1—Distribution of glucose readings during the 24-h CGMS measurement at baseline (A; week 0), on-treatment (B; week 4), and off-treatment (C; week 6).

Postprandial plasma glucose, glucagon, and triglyceride excursions

Results from the postprandial plasma glucose, glucagon, and triglyceride excursions are depicted in Fig. 3A–C. During the baseline period, the AUC for postprandial glucose was $184 \pm 195 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$ (mean incremental $\text{AUC}_{0-3 \text{ h}}$). After

4 weeks of pramlintide treatment, the mean incremental $\text{AUC}_{0-3 \text{ h}}$ for postprandial glucose was reduced by 86% (to $26 \pm 101 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$; $P < 0.05$). At week 6 (off-treatment), the mean incremental AUC for postprandial plasma glucose approached baseline values ($139 \pm 147 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$).

During the baseline period, the AUC for postprandial glucagon was $55 \pm 44 \text{ pg} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$ (mean incremental $\text{AUC}_{0-3 \text{ h}}$). After 4 weeks of pramlintide treatment, the mean incremental AUC for postprandial plasma glucagon was reduced by 87% (to $7 \pm 38 \text{ pg} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$; $P < 0.05$). At week 6 (off-treatment), the

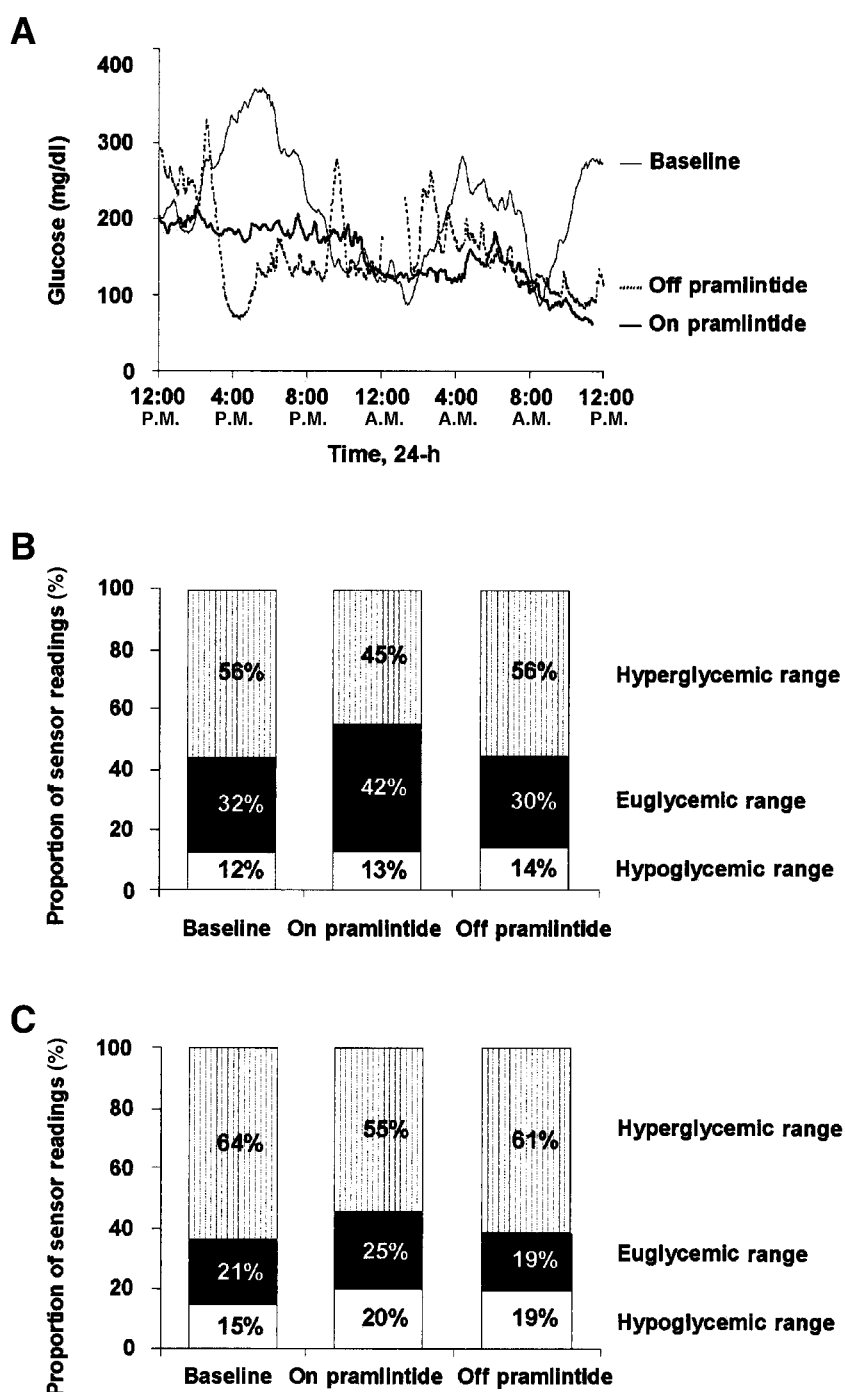


Figure 2—A: An individual 24-h CGMS reading showing reduced 24-h glucose fluctuations, including postprandial glucose spikes, after 4 weeks on pramlintide (week 4) compared to CSII alone (weeks 0 and 6). The subject was a male, age 43, with type 1 diabetes and an HbA_{1c} of 8.4%. (Conversion to SI units: value \times 0.055.) B and C: Proportion of 24-h glucose readings falling above (>140 mg/dl), below (<80 mg/dl), or within the euglycemic target range (80–140 mg/dl) during the daytime (B; 6:00 A.M. to 10:00 P.M.), and nighttime (C; 10:00 P.M. to 6:00 A.M.), at baseline (week 0), on-treatment (week 4), and off-treatment (week 6).

mean incremental AUC for postprandial glucagon approached baseline values (31 ± 44 pg \cdot ml⁻¹ \cdot h⁻¹).

During the baseline period, the AUC for postprandial plasma triglyceride was 66 ± 88 mg \cdot dl⁻¹ \cdot h⁻¹ (mean incre-

mental AUC_{0–3 h}). After 4 weeks of pramlintide treatment, the mean incremental AUC for postprandial plasma triglyceride was reduced by 72% (to 18 ± 58 mg \cdot dl⁻¹ \cdot h⁻¹, $P < 0.05$). At week 6 (off-treatment), the mean incremental AUC for postprandial plasma triglyceride response approached baseline values (56 ± 85 mg \cdot dl⁻¹ \cdot h⁻¹).

Serum fructosamine concentration

Mean serum fructosamine concentrations declined by 6% from baseline to week 4 (from 341 to 321 μ mol/l; $P < 0.05$) and returned to baseline values at week 6 (343 μ mol/l).

Safety

Consistent with the results of previous randomized, double-blind, placebo-controlled multicenter studies in larger numbers of patients with type 1 diabetes (20,22,23), there was no evidence of toxicity to any of the major organ systems. Moreover, there were no clinically relevant changes in laboratory tests, vital signs, electrocardiograms, or abnormal findings upon physical examinations. Mild-to-moderate nausea was the most commonly reported adverse event. No severe hypoglycemic events occurred during the study.

CONCLUSIONS— Previous randomized, double-blind, placebo-controlled, clinical trials in patients with type 1 diabetes have shown that mealtime amylin replacement with pramlintide, as an adjunct to insulin therapy, facilitates a significant further improvement in postprandial (17,20) and long-term overall glycemic control (HbA_{1c}). This is accompanied by weight loss rather than weight gain and occurs without a sustained increase in the risk of severe hypoglycemia (21–23).

The results of the present study indicate that adjunctive treatment with pramlintide may have at least two additional clinical benefits in patients with type 1 diabetes; namely, a reduction of excessive 24-h glucose fluctuations and of postprandial triglyceride excursions.

The results of our baseline CGMS measurements confirmed the results of other recent studies with the CGMS (2,5), showing that patients with type 1 diabetes, even those who are intensively treated and in seemingly good glycemic control (based on HbA_{1c} values), have excessive

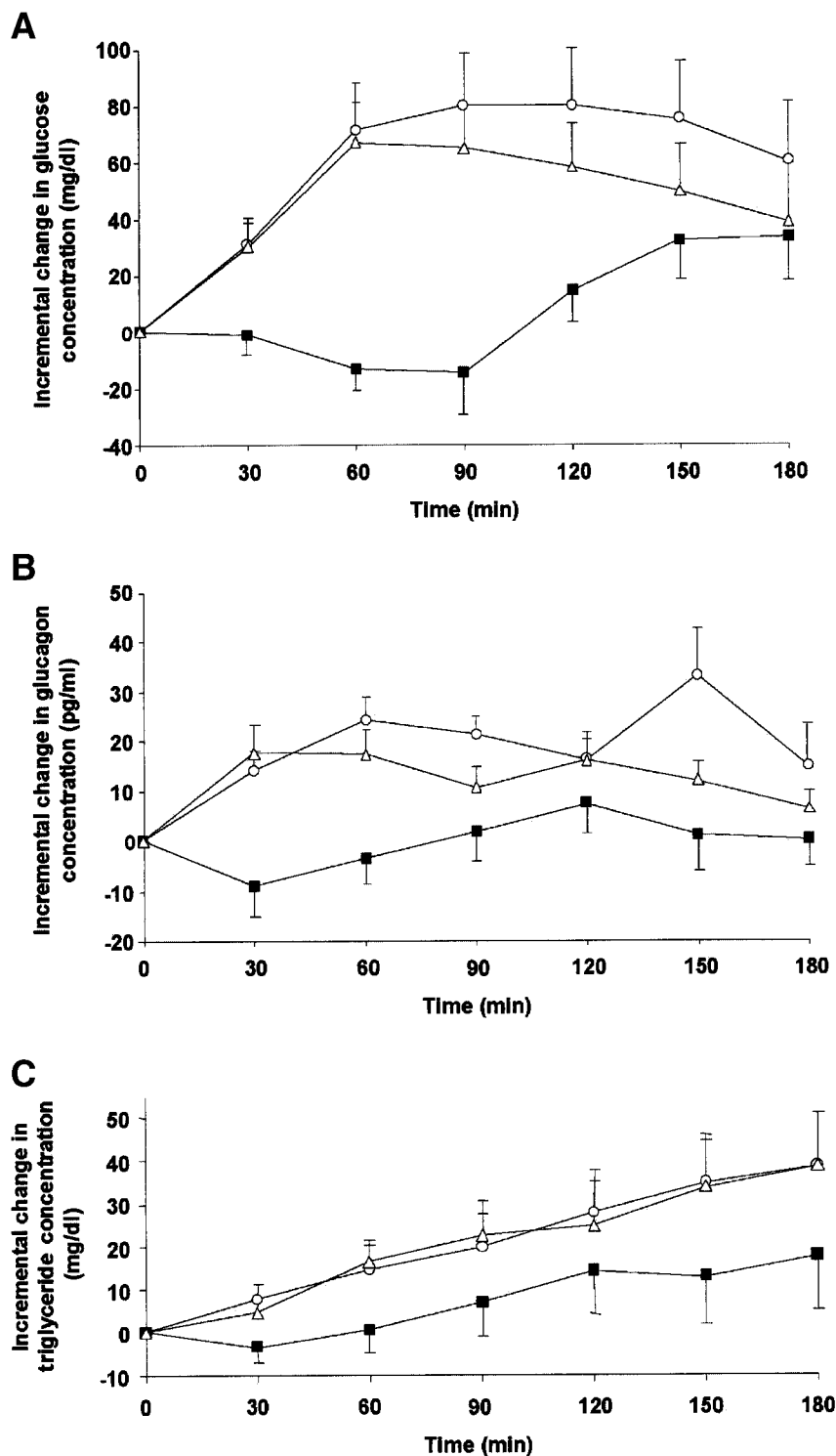


Figure 3—Postprandial plasma (A) glucose (conversion to SI units: value $\times 0.055$.), (B) glucagon, and (C) triglyceride excursions at baseline (○, week 0), on-treatment (■, week 4), and off-treatment (△, week 6). P values provided in RESULTS.

glucose fluctuations, with numerous hyperglycemic peaks and often unrecognized hypoglycemic episodes. Based on this finding, it has been proposed that the

24-h glucose profile obtained with the CGMS may be a clinically useful tool to guide adjustments to the therapeutic regimen (5,7).

When the CGMS measurements were repeated after 4 weeks of pramlintide treatment, glucose fluctuations were clearly reduced. Specifically, the time patients spent with glucose values in the hyperglycemic range had decreased, a finding consistent with the well-documented postprandial glucose-lowering effect of pramlintide in patients with type 1 diabetes (17,20). Conversely, the percent of glucose readings in the euglycemic target range had increased by 32% after 4 weeks of pramlintide treatment. Importantly, the observed shift of glucose readings from the hyperglycemic to the euglycemic target range with pramlintide was accompanied by virtually no increase in sensor readings below the euglycemic range. This observation is consistent with pramlintide's mechanism of action being anti-hyperglycemic, and not hypoglycemic, as is the case with insulin (10,11,14). Increased hypoglycemia is commonly seen when glucose control is improved by simply increasing the insulin dosage. In the present study, mealtime insulin dosages were proactively reduced by at least 10% upon initiation of pramlintide treatment and remained 17% lower at the end of the 4-week treatment period. With the insulin reduction at the initiation of pramlintide, no severe hypoglycemic events occurred, indicating that pramlintide treatment can be safely introduced in intensively treated patients with type 1 diabetes.

Although the CGMS device used in the present study has been widely applied in the clinical setting, experience with this device as a tool for clinical research is still limited. To our knowledge, the present study represents the first report where this technology has been applied to examine the effect of a novel pharmacological intervention on glucose fluctuations in patients with diabetes. To minimize the methodological limitations of the CGMS, such as calibration drifts and sensor failures, we implemented a blinded data review process that allowed sensor measurements to be repeated if data quality was poor. By using this approach, we were able to obtain acceptable sensor data from all patients.

Previous studies examining the effect of pramlintide on postprandial glucose excursions have included mainly patients using regular insulin (17,20). The results of the present study show that pramlintide also improves postprandial glucose

excursions in patients who are intensively treated with CSII and predominantly rapid-acting insulin analogs. This is consistent with insulin and amylin playing complementary roles in postprandial glucose homeostasis; that is, pramlintide reduces postprandial glucose excursions by mechanisms distinct from those of insulin and its analogs (10,11,14).

The observed suppression of postprandial glucagon concentrations during pramlintide treatment is one of these mechanisms. With current forms of subcutaneous insulin therapy, even intensively treated, well-controlled patients with type 1 diabetes have an abnormal portal vein (and therefore hepatic sinusoidal) glucagon-to-insulin ratio, particularly during the postprandial period. This is attributable not only to a failure to achieve the normally high portal vein insulin concentrations with subcutaneously injected insulin, but also to the fact that many patients with type 1 diabetes have an impaired suppression of, or even a paradoxical increase in, glucagon concentrations postprandially (24). By virtue of its dual effect on postprandial glucagon secretion (17,18) and gastric emptying (19), pramlintide helps reduce the rate of endogenous (liver-derived) and exogenous (meal-derived) glucose inflow into the bloodstream to a rate that better matches the rate of insulin-mediated glucose disposal, thereby reducing postprandial glucose excursions (11). The addition of pramlintide to insulin therapy may therefore be a valuable means of optimizing postprandial glucose control regardless of the type of insulin used.

Another interesting finding was that the addition of pramlintide to insulin therapy also reduced postprandial triglyceride excursions, an effect that might be attributable to pramlintide's effect on gastric emptying. By slowing the delivery of all nutrients (carbohydrates, lipids, and proteins) from the stomach to the small intestine (11,19), pramlintide likely tempers not only the inflow of glucose into the circulation, but also the inflow of chylomicrons and other meal-derived lipoproteins. This may help to better match the patients' capacity for lipoprotein clearance, thereby limiting the postprandial triglyceride excursion. Given that many patients with diabetes experience postprandial hyper- and dyslipidemia, and that this abnormality has been implicated as a potential cardiovascular risk

factor (25,26), additional studies are warranted to further examine the postprandial lipid-lowering effect of pramlintide.

In conclusion, the results of this study indicate that in the setting of intensive insulin therapy, replacement of amylin with pramlintide reduces excessive 24-h glucose fluctuations and postprandial glucose excursions in patients with type 1 diabetes, which may help those patients more safely achieve glycemic goals.

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