# Pramlintide, a Synthetic Analog of Human Amylin, Improves the Metabolic Profile of Patients With Type 2 Diabetes Using Insulin

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**OBJECTIVE** — To examine the effects of 4 weeks of subcutaneous administration of pramlintide, a synthetic analog of human amylin, on metabolic control in patients with type 2 diabetes using insulin.

**RESEARCH DESIGN AND METHODS** — Serum fructosamine, $HbA_{1c}$, and fasting plasma lipids were measured in 203 patients in a randomized double-blind placebo-controlled parallel-group multicenter trial using doses of 30 μg q.i.d., 60 μg t.i.d., and 60 μg q.i.d.

**RESULTS** — Statistically significant reductions in serum fructosamine concentrations were observed in the pramlintide 30 μg q.i.d. group (17.5 ± 4.9 μmol/l, $P = 0.029$), the pramlintide 60 μg t.i.d. group (24.1 ± 4.9 μmol/l, $P = 0.003$), and the 60 μg q.i.d. group (22.6 ± 4.1 μmol/l, $P = 0.001$) compared with the placebo group (3.5 ± 3.8 μmol/l). There were also statistically significant shifts in the proportion of patients with an abnormal serum fructosamine concentration at baseline that normalized at week 4 within the pramlintide 60 μg t.i.d. group and the 60 μg q.i.d. group. Consistent with the fructosamine results, there were statistically significant reductions in $HbA_{1c}$ in the pramlintide 30 μg q.i.d. group (0.53 ± 0.07%, $P = 0.0447$), the pramlintide 60 μg t.i.d. group (0.58 ± 0.07%, $P < 0.0217$), and the pramlintide 60 μg q.i.d. group (0.51 ± 0.08%, $P = 0.0242$) compared with the placebo group (0.27 ± 0.08%). Total cholesterol concentrations were also statistically significantly reduced in both the pramlintide 60 μg t.i.d. group (8.4 mg/dl, $P < 0.01$) and 60 μg q.i.d. group (10.5 mg/dl, $P < 0.01$) compared with placebo (1.2 mg/dl). Body weight decreased in both of the pramlintide 60 μg groups, but the trend did not achieve statistical significance. The incidence of hypoglycemia was similar in all treatment groups.

**CONCLUSIONS** — Reductions in serum fructosamine, plasma total and LDL cholesterol concentrations, and $HbA_{1c}$ support the hypothesis that pramlintide may improve metabolic control in patients with type 2 diabetes using insulin.

Amylin is a recently discovered 37–amino acid peptide hormone that is copackaged and cosecreted with insulin by pancreatic β-cells in response to nutrient stimuli (1). Actions of amylin or pramlintide, a synthetic analog of human amylin, include limiting food intake, possibly through a central mechanism (2–4), controlling gastric motility (5,6), and suppressing postprandial glucagon secretion (7–9), which may reduce postprandial hepatic glucose production.

Notably, pramlintide does not reduce the increase in glucagon seen in response to hypoglycemia (10). The action of amylin on gastric emptying is also reversed by insulin-induced hypoglycemia, suggesting the existence of a glucose-sensitive override mechanism that guards against severe hypoglycemia (11). All of these actions have been demonstrated with amylin or pramlintide administration that achieves circulating concentrations mimicking amylin concentrations reported in healthy subjects. Thus, amylin appears to contribute to the maintenance of normal glucose homeostasis through these actions that reduce the rate of nutrient influx during the postprandial period and, thus, complement the glucose disposal actions of insulin.

In healthy subjects, 24-h plasma profiles of amylin and insulin reveal similar secretion patterns in response to nutrient ingestion (12). In people with type 1 diabetes, who are β-cell deficient, plasma amylin concentrations fall below the limits of assay detection (13). Consistent with the β-cell failure known to accompany disease progression, plasma concentrations of both insulin and amylin are reduced in people with late-stage type 2 diabetes; amylin secretion appears to be delayed and diminished in this population (14).

Pramlintide is a synthetic analog of human amylin that has the desired biologic actions of human amylin, but it is substantially different from and better than amylin. By way of example, it is readily soluble in water, and it does not stick to surfaces, aggregate, or form insoluble particles as amylin does. Studies with pramlintide in patients with type 1 diabetes demonstrated statistically significant reductions in postprandial plasma glucose after either intravenous infusion (15) or 14 days of subcutaneous administration of pramlintide (16). Recently, it was demonstrated that 4 weeks of subcutaneous administration of pramlintide to patients with type 1 diabetes produced statistically significant reductions in the 24-h plasma glucose profile (17) and in serum fructosamine concentrations (18). Because of these promising results in patients with type 1 diabetes, clinical studies in patients with type 2 diabetes who use insulin were undertaken to determine whether the addition of pramlintide to insulin regimens could improve metabolic control.

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Received for publication 5 August 1997 and accepted in revised form 18 February 1998.
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**Abbreviations:** ANOVA, analysis of variance.

The present study was designed as a double-blind randomized placebo-controlled parallel-group trial to examine the effects of 4 weeks of subcutaneous pramlintide administration on indicators of metabolic control in patients with type 2 diabetes using insulin. Three pramlintide dosing regimens were compared with placebo to ascertain their effect on serum fructosamine concentrations, $HbA_{1c}$, and serum lipids. Safety and tolerability were also assessed.

## RESEARCH DESIGN AND METHODS

### Patients

Study participants were men and women, 25–78 years of age, with a history of type 2 diabetes according to World Health Organization diagnostic criteria, who were using insulin for at least 6 months before the prescreening visit. $HbA_{1c}$ values were <13% in all patients. Patients were negative for serum hepatitis B surface antigen and had body weights varying not more than 45% from the desirable weight before admission into the study (based upon Metropolitan Life Tables).

### Study design

Institutional review boards approved all procedures, and a signed consent was obtained at the initial visit. Physical examination, blood chemistry, hematology, and urinalysis were performed at the initial visit, in addition to blood sampling for serum fructosamine and $HbA_{1c}$ concentrations. Patients who satisfied the inclusion criteria and met the screening requirements returned to the clinic within 21 days to begin the 8-day single-blind placebo lead-in period.

After the placebo lead-in period, patients were randomized to receive placebo or one of three dose regimens of pramlintide for 4 weeks: 30 μg q.i.d. (before breakfast, lunch, dinner, and evening snack), 60 μg t.i.d. (before breakfast, lunch, and dinner), or 60 μg q.i.d. (before breakfast, lunch, dinner, and evening snack). Throughout the study-drug period, patients self-administered four injections of the study drug daily, within 15 min of each meal and the evening snack. During the double-blind period, patients randomized to pramlintide 60 μg t.i.d. administered placebo before the evening snack. To accomplish this, patients were provided with four vials to be used each day, with each vial designated for a specific injection time. Both pramlintide and placebo were administered as separate injections into the subcutaneous tissue of the anterior abdominal wall; the specific site was alternated after each injection.

Patients were instructed to remain on their usual diet, insulin, and exercise regimens throughout the study, unless otherwise instructed by the investigator, and to abstain from alcoholic beverages before all clinic visits. Each patient monitored and kept a diary of preprandial and bedtime blood glucose concentrations, daily insulin requirements, hypoglycemic signs and symptoms, and dietary supplements (snacks) throughout the placebo lead-in and double-blind phases of the trial. Patients reported to the clinic a total of six times, including the screening visit. At each clinic visit, the investigator determined whether any adverse events had occurred and recorded this information.

### Placebo lead-in period

On the first day of the placebo lead-in period (study day 1), patients returned to the clinic and were instructed in study drug administration, diary card completion, and the use of a glucose meter. Patients then began 8 days of single-blind placebo four-times-a-day administration.

### Study-drug period

On study day 9, patients were randomized, had an abbreviated physical examination, and began 28 days of double-blind study drug administration. On study days 15 and 22, patients returned to the clinic for an interim history and abbreviated physical examination. Routine safety laboratories were also drawn on study day 15. On study day 36, samples for serum fructosamine measurements and routine laboratory tests were collected, and patients had a physical examination, interim history, and were discontinued from the study drug.

### Measurements

**Serum fructosamine concentration.** Blood was collected in serum separator tubes and allowed to clot for 30 min for measurement of serum fructosamine concentration along with other blood chemistry parameters. Serum fructosamine concentration was measured by Corning SciCor Laboratories (Indianapolis, IN) using the RoTAG colorimetric assay based on the Baker nitroblue tetrazolium method. The normal reference values for the assay range up to 285 μmol/l.

**$HbA_{1c}$.** Whole blood samples containing EDTA were hemolyzed for the $HbA_{1c}$ assay. $HbA_{1c}$ was measured by Corning SciCor Laboratories using the BioRad Variant high-performance liquid chromatography system, with a detection limit of 3.6%. The normal reference range for the assay is 4.30–6.10%.

**Serum lipids.** Whole blood samples were drawn into serum separator tubes for measurements of total cholesterol, HDL cholesterol, LDL cholesterol, HDL:LDL cholesterol ratio, and triglycerides by Corning SciCor Laboratories.

### Statistical analysis

An evaluable patient for the fructosamine and $HbA_{1c}$ analysis was one who had results at both the baseline visit and after 4 weeks of double-blind study drug administration. For continuous normally distributed variables, a two-way analysis of variance (ANOVA) with the Hochberg adjustment for multiple comparisons (19) was used for between-group comparisons, and the Student's *t* test was used for within-group comparisons. For continuous non-normally distributed variables, a Wilcoxon rank-sum test with the Hochberg adjustment for multiple comparisons was used for between-group comparisons, and a Wilcoxon signed-rank test was used for within-group comparisons. For categorical variables, a $\chi^2$ test was used for between-group comparisons, and McNemar's test was used for within-group comparisons. Results that were evaluated as change from baseline after 4 weeks of double-blind study drug administration were calculated by subtracting the 4-week results from the baseline results. For the fructosamine analysis, screening results were defined as baseline.

## RESULTS

### Patient disposition

There were 203 patients randomized, and 197 patients completed the study. There were 194 evaluable patients for the fructosamine analysis and 193 evaluable patients for the $HbA_{1c}$ analysis.

### Demographic characteristics

The baseline demographic characteristics of the randomized patients are presented in Table 1. There were no statistically significant differences in demographic characteristics among the treatment groups. Approximately 50% (46–54%) of the

Table 1—*Demographic characteristics of randomized patients*

| | Placebo | Pramlintide 30 µg q.i.d. | Pramlintide 60 µg t.i.d. | Pramlintide 60 µg q.i.d. |
|---|---|---|---|---|
| *n* | 50 | 49 | 50 | 54 |
| Age (years) | 57.5 ± 1.5 (25–74) | 60.2 ± 1.3 (39–73) | 58.9 ± 1.5 (33–78) | 59.6 ± 1.4 (33–75) |
| BMI (kg/m²) | 30.5 ± 0.7 (20–42) | 30.6 ± 0.7 (18–42) | 29.8 ± 0.6 (21–41) | 31.7 ± 0.8 (20–47) |
| Weight (kg) | 87.2 ± 2.4 (58–131) | 88.5 ± 2.6 (48–140) | 86.0 ± 2.3 (56–126) | 92.1 ± 2.4 (52–127) |
| Time since initiation of diet or oral hypoglycemic agent therapy (years) | 11.3 ± 1.1 (0.5–36) | 10.6 ± 1.1 (0.75–41) | 8.4 ± 0.9 (0.58–22.4) | 11.8 ± 1.1 (0–40) |
| Duration of insulin therapy (years) | 7.5 ± 1.1 (0.8–34) | 6.3 ± 0.8 (0.6–22) | 4.4 ± 0.5* (0.5–16) | 5.3 ± 0.7 (0.6–25) |

Data are means ± SEM (range). For weight, *n* = 48 (placebo); 47 (pramlintide 30 µg q.i.d.); 50 (pramlintide 60 µg t.i.d.); and 52 (pramlintide 60 µg q.i.d.). *Significantly different from placebo (one-way ANOVA).

patients in each group were men. The majority of patients in each treatment group were Caucasian. The duration of insulin treatment was statistically significantly shorter in the pramlintide 60 µg t.i.d. group than in the placebo group ($P$ = 0.0056). There were no other statistically significant differences in the duration of type 2 diabetes, as ascertained by history between treatment groups.

### Baseline comparability of the treatment groups

There were no statistically significant differences at baseline in serum fructosamine, $HbA_{1c}$, or total daily insulin administered between any pramlintide group and the placebo group. The correlation between baseline $HbA_{1c}$ and baseline serum fructosamine concentrations was $r$ = 0.62.

### Serum fructosamine concentration

As shown in Fig. 1, the mean serum fructosamine concentration was statistically significantly reduced from baseline to week 4 in the pramlintide 30 µg q.i.d., 60 µg t.i.d., and 60 µg q.i.d. groups compared with placebo. The reduction in serum fructosamine concentration from baseline to week 4 was also statistically significant within each of the three pramlintide groups (30 µg q.i.d., $P$ = 0.0009; 60 µg t.i.d., $P$ = 0.0001; 60 µg q.i.d., $P$ = 0.0001) but not within the placebo group.

The number of patients with shifts in their serum fructosamine concentrations from abnormal (>285 µmol/l) at baseline to normal (≤285 µmol/l) at week 4 and from normal at baseline to abnormal at week 4 was also evaluated. Figure 2 presents the proportion of patients with these shifts in serum fructosamine concentrations in each treatment group. The proportion of patients with an abnormal serum fructosamine concentration at baseline that normalized at week 4 was statistically significant within both the pramlintide 60 µg q.i.d. and pramlintide 60 µg t.i.d. groups. The remaining patients did not change from one category to another category.

### $HbA_{1c}$ value

As shown in Fig. 3, the mean $HbA_{1c}$ concentration was statistically significantly reduced from baseline to week 4 in the pramlintide 30 µg q.i.d., 60 µg t.i.d., and 60 µg q.i.d. groups compared with placebo. The reduction in $HbA_{1c}$ from baseline to week 4 was also statistically significant within each of the three pramlintide groups ($P$ = 0.0001 for each group) as well as within the placebo group ($P$ = 0.0008).

### Fasting lipids

Table 2 presents both the mean fasting lipid concentrations at baseline and the reduction in the mean fasting lipid concentrations from baseline to week 4. The reduction in fasting total cholesterol from baseline to week 4 was statistically significant in the pramlintide 60 µg t.i.d. and pramlintide 60 µg q.i.d. groups compared with the placebo group. The reduction in the mean fasting total cholesterol from baseline to week 4 was also statistically significant within each of the three pramlintide groups but not within the placebo group.

In contrast, there were no statistically significant changes in fasting LDL cholesterol, HDL cholesterol, triglyceride concentrations, or the HDL:LDL cholesterol ratio from baseline to week 4 in any of the three

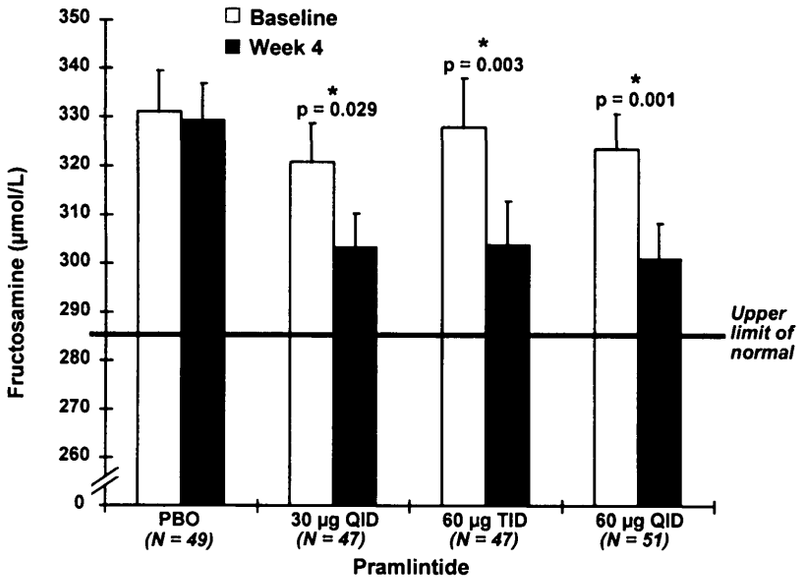


**Figure 1**—*Change in serum fructosamine concentration from baseline to week 4 for the placebo, pramlintide 30 µg q.i.d., pramlintide 60 µg t.i.d., and pramlintide 60 µg q.i.d. groups. *Statistically significant difference compared with the placebo group.*

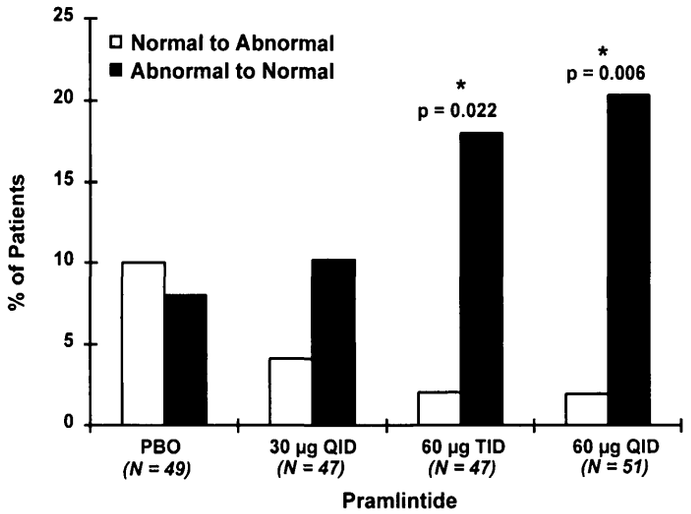


**Figure 2**—*Patients with shifts in serum fructosamine concentration from baseline to week 4 for all four treatment groups. Values are expressed as a percentage of the total number of patients in each treatment group. *Statistically significant within-group comparison for normalization of serum fructosamine concentration.*

pramlintide groups compared with the placebo group. There was a statistically significant reduction in LDL cholesterol from baseline to week 4 within the pramlintide 60 µg t.i.d. and pramlintide 60 µg q.i.d. groups, but not within the pramlintide 30 µg q.i.d. or placebo groups. There were no statistically significant changes in HDL cholesterol or in the HDL:LDL cholesterol ratio within any treatment groups. Although triglyceride results did not achieve statistically significant differences, a higher incidence of patients receiving pramlintide started with concentrations >200 mg/dl and had concentrations <200 mg/dl at the end of treatment (3 of 11 for 30 µg t.i.d. and 6 of 17 for each of the 60 µg groups).

### Body weight

There was a statistically significant reduction in body weight from baseline to week 4 within the pramlintide 60 µg t.i.d. and pramlintide 60 µg q.i.d. groups, but not within the pramlintide 30 µg q.i.d. group or the placebo group (Table 3). With the Hochberg adjustment for multiple comparisons, there was no statistically significant change in body weight from baseline to week 4 in any of the three pramlintide groups compared with the placebo group.

### Insulin use

There were no statistically significant changes from baseline to week 4 in total daily insulin administered within any of the pramlintide treatment groups or the placebo group based upon patient diaries. There also were no statistically significant differences in reported total daily insulin administered between the pramlintide and placebo groups.

### Safety data

Gastrointestinal adverse events occurred more frequently in patients in the pramlintide groups than in patients in the placebo group. The most frequently reported gastrointestinal adverse event in the three pramlintide groups was nausea; the incidence was similar among the three pramlintide groups (10–14%), while nausea did not occur in the placebo group. Most gastrointestinal adverse events were reported during the initial 2 weeks of double-blind study medication. In particular, nausea was transient, as it was reported by 11% of patients in the pramlintide groups during the first 2 weeks of the study but by only 2% of patients in these groups during the second 2 weeks of the study. The incidence of hypoglycemia was no greater in any pramlintide group (2%) than in the placebo group (6%).

**CONCLUSIONS** — When managing patients with type 2 diabetes, in whom complications resulting from atherosclerotic cardiovascular disease are the major source of morbidity and mortality, the desired outcome is an improved metabolic profile, including improved glycemic control and reductions in body weight and plasma lipids. In the present study, the addition of the synthetic amylin analog pramlintide to the existing insulin regimens of patients with type 2 diabetes for 28 days resulted in significant improvements in the metabolic profiles of the participants.

Many investigators (20–24) have used serum fructosamine concentrations as an indicator of short-term (25,26) glycemic control in patients with diabetes. Mean serum fructosamine concentrations and $HbA_{1c}$ values were reduced after 4 weeks of pramlintide administration compared with

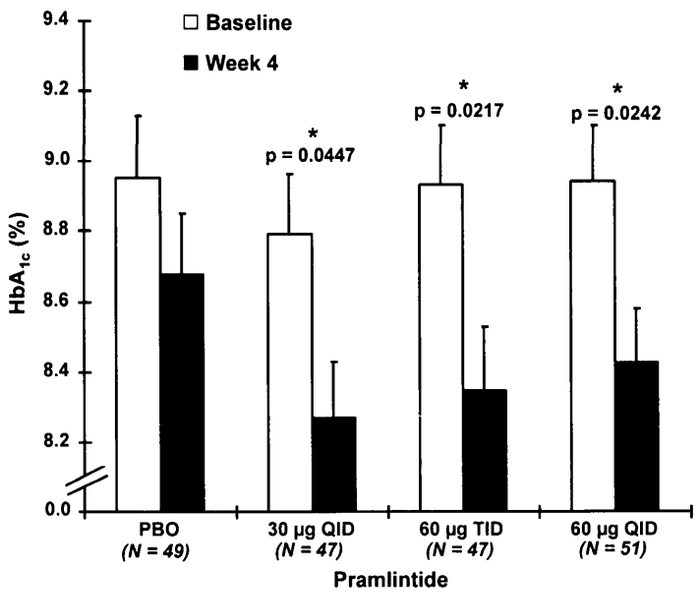


**Figure 3**—*Change in $HbA_{1c}$ from baseline to week 4 for the placebo, pramlintide 30 µg q.i.d., pramlintide 60 µg t.i.d., and pramlintide 60 µg q.i.d. groups. *Statistically significant difference compared with the placebo group.*

**Table 2—*Change in fasting total, LDL, and HDL cholesterol, and triglycerides***

| | *n* | Mean baseline | Change at week 4 | |
|---|---|---|---|---|
| | | | Mean | Median |
| Total cholesterol (mg/dl) | | | | |
| Placebo | 43 | 197.77 | 1.19 | 0.0 |
| Pramlintide 30 μg q.i.d. | 44 | 204.84 | −4.73 | −9.0* |
| Pramlintide 60 μg t.i.d. | 43 | 203.81 | −8.35 | −9.0†§ |
| Pramlintide 60 μg q.i.d. | 46 | 216.78 | −10.46 | −14.0†‡ |
| LDL cholesterol (mg/dl) | | | | |
| Placebo | 40 | 121.15 | −2.05 | −2.0 |
| Pramlintide 30 μg q.i.d. | 39 | 130.10 | −4.41 | −8.0 |
| Pramlintide 60 μg t.i.d. | 38 | 130.55 | −5.42 | −8.0‖ |
| Pramlintide 60 μg q.i.d. | 40 | 131.68 | −7.50 | −10.0‖ |
| HDL cholesterol (mg/dl) | | | | |
| Placebo | 43 | 42.67 | 0.65 | 1.0 |
| Pramlintide 30 μg q.i.d. | 44 | 41.30 | −0.70 | 0.0 |
| Pramlintide 60 μg t.i.d. | 43 | 40.12 | −0.86 | 0.0 |
| Pramlintide 60 μg q.i.d. | 45 | 42.07 | −0.51 | 0.0 |
| HDL:LDL cholesterol ratio | | | | |
| Placebo | 40 | 0.37 | 0.01 | 0.01 |
| Pramlintide 30 μg q.i.d. | 39 | 0.34 | 0.01 | 0.01 |
| Pramlintide 60 μg t.i.d. | 38 | 0.33 | 0.01 | 0.01 |
| Pramlintide 60 μg q.i.d. | 40 | 0.35 | 0.01 | 0.01 |
| Triglycerides (mg/dl) | | | | |
| Placebo | 43 | 163.60 | 22.05 | 9.0 |
| Pramlintide 30 μg q.i.d. | 44 | 178.46 | 7.02 | 3.0 |
| Pramlintide 60 μg t.i.d. | 43 | 200.05 | −8.95 | −7.0 |
| Pramlintide 60 μg q.i.d. | 46 | 250.28 | −66.37 | 0.5 |

*Statistically significant difference within study-drug group (signed-rank test; $P < 0.05$); †$P < 0.01$; ‡statistically significant difference compared with placebo (Wilcoxon's rank-sum test with the Hochberg adjustment; $P < 0.05$); §$P < 0.01$; ‖statistically significant difference within study-drug group (Student's *t* test; $P < 0.05$).

placebo in the patients with type 2 diabetes treated with insulin who participated in this study. Statistically significant reductions in mean serum fructosamine concentrations were observed in all three pramlintide groups (30 μg q.i.d., 60 μg t.i.d., and 60 μg q.i.d.) compared with placebo. Furthermore, within the pramlintide 60 μg t.i.d. and 60 μg q.i.d. groups, there were statistically significant shifts in the proportion of patients with an abnormal serum fructosamine concentration at baseline to a normal serum fructosamine concentration at week 4. The reductions in serum fructosamine were paralleled by statistically significant reductions in $HbA_{1c}$ in all three pramlintide groups compared with placebo.

Based on plasma half-lives, the changes in fructosamine observed should have stabilized by the end of the 28-day observation period. In contrast, $HbA_{1c}$ values require 90–120 days to equilibrate after a significant modification in glycemic control has been achieved. Thus, the observed reductions in $HbA_{1c}$ would likely increase over longer periods of administration, provided that the therapeutic effect is sustained.

The improvement in glycemic control observed when pramlintide was added to the patients' usual insulin regimens was associated with a decrease in body weight that achieved statistical significance within the 60 μg t.i.d. and q.i.d. groups. Although this decrease in body weight did not reach statistical significance compared with the placebo group, the trends are suggestive and, if maintained during longer periods of treatment, could add benefit in the management of these patients. This decrease is in sharp contrast to weight gain usually associated with the improved glucose control achieved by increasing doses of insulin in patients with type 2 diabetes (27).

In addition, a statistically significant reduction in the mean fasting total cholesterol concentration was observed after 4 weeks of administration of pramlintide 60 μg t.i.d. and 60 μg q.i.d. Furthermore, in these groups, there was a trend toward a reduction in fasting LDL cholesterol that achieved statistical significance in within-group comparisons. HDL and HDL:LDL cholesterol ratios did not change as a result of therapy. Triglyceride concentrations showed greater variability and, while the mean values for the respective treatment groups did not change significantly, a greater number of patients within the pramlintide treatment groups with elevated values at baseline exhibited reductions during treatment compared with the placebo group.

As in previous pramlintide studies conducted in patients with type 1 diabetes (16–18), transient nausea was the side effect that occurred most frequently in patients in the pramlintide groups. This nausea was not disabling in the vast majority of patients and usually subsided within 1 or 2 weeks of initiation of pramlintide therapy. Also, as in previous studies (16–18), the improvement in glycemic control observed in the three pramlintide treatment groups was achieved without an increase in either the incidence or severity of hypoglycemia. Based on these observations, the very favorable safety profile of pramlintide observed previously in patients with type 1 diabetes appears to extend to patients with type 2 diabetes using insulin.

The mechanism(s) responsible for the improvement in metabolic control contributed by pramlintide is not fully defined. However, the observations presented here are consistent with the evolving understanding of amylin as a neuroendocrine

**Table 3—*Change in body weight***

| Treatment group | *n* | Mean baseline (kg) | Mean change at week 4 (kg) |
|---|---|---|---|
| Placebo | 47 | 87.0 | −0.04 |
| Pramlintide 30 μg q.i.d. | 47 | 88.5 | −0.36 |
| Pramlintide 60 μg t.i.d. | 48 | 86.2 | −0.89* |
| Pramlintide 60 μg q.i.d. | 51 | 91.5 | −0.72* |

*Statistically significant within study group (Student's *t* test; $P < 0.01$).

peptide that is secreted peripherally and exerts its effects via centrally mediated mechanisms involving selective binding sites in the area postrema (28). This region of the brain is thought to regulate gastrointestinal motility, consistent with the reported effects of amylin and pramlintide to reduce the rate of gastric emptying in animals (5) and humans (6), respectively. Recent studies suggest that this effect, which contributes to reduced postprandial glucose concentrations, is dependent upon an intact vagus nerve (29).

The area postrema has also been implicated recently in the regulation of satiety and food intake in rats (2,4). The observed trends in body weight in the pramlintide treatment group are consistent with decreased food intake. However, additional studies of longer duration are required to evaluate the potential effect.

Recently, pramlintide administration has been shown to decrease postprandial glucagon concentrations in patients with type 1 diabetes (8,9). Postprandial glucagon concentrations have been shown to be elevated in both type 1 and type 2 diabetes, and are felt to contribute to the increased rates of hepatic glucose output observed in these subjects during the postprandial period. Thus, the reduction in postprandial plasma glucose concentrations observed after pramlintide administration likely represents the combined effects of reduced rates of gastric emptying and reduced postprandial glucagon concentrations. Although not assessed to date, the reduced rates of gastric emptying may also result in reduced plasma triglyceride concentrations during the postprandial period. This perturbation in lipid homeostasis may, in turn, translate into the modest reductions observed in fasting total and LDL cholesterol concentrations.

In summary, 4 weeks of self-administered pramlintide significantly reduced serum fructosamine concentration and $HbA_{1c}$ in patients with type 2 diabetes treated with exogenous insulin. These results are consistent with and expand on previous studies characterizing pramlintide activity in improving glycemic control in patients with type 1 diabetes (16–18). The reductions in serum fructosamine concentration and $HbA_{1c}$ were accompanied by a reduction in fasting total cholesterol and a trend toward decreased body weight. These beneficial metabolic effects were achieved without an increase in the incidence of hypoglycemia. Additional studies are underway assessing both the safety and magnitude of these effects during longer periods of treatment.

**Acknowledgments**— We gratefully acknowledge the investigators in the Pramlintide in Type 2 Diabetes Group who completed this multicenter trial (see APPENDIX).

The staff of Hurley Consulting Associates, Chatham, NH, provided valuable support in data management, statistical analysis, and helpful comments throughout the conduction of this study.

## APPENDIX

### The Pramlintide in Type 2 Diabetes Group

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