Pramlintide as an Adjunct to Insulin Therapy Improves Long-Term Glycemic and Weight Control in Patients With Type 2 Diabetes

A 1-year randomized controlled trial

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OBJECTIVE — Mealtime amylin replacement with the human amylin analog pramlintide, as an adjunct to mealtime insulin replacement, reduces postprandial glucose excursions in patients with type 2 diabetes. The aim of the present study was to assess the long-term efficacy and safety of pramlintide in this patient population.

RESEARCH DESIGN AND METHODS — In a 52-week, double-blind, placebo-controlled, parallel-group, multicenter study, 656 patients with type 2 diabetes (age 57 ± 10 years, diabetes duration 12 ± 7 years, BMI 34.0 ± 7.0 kg/m^2, HbA_{1c} 9.1 ± 1.2%, mean ± SD) treated with insulin (alone or in combination with sulfonylureas and/or metformin) were randomized to receive additional preprandial subcutaneous injections of either placebo or pramlintide (60 μg TID, 90 μg BID, or 120 μg BID).

RESULTS — Treatment with pramlintide 120 μg BID led to a sustained reduction from baseline in HbA_{1c} (−0.68 and −0.62% at weeks 26 and 52, respectively), which was significantly greater than that seen with placebo ($P < 0.05$). The proportion of patients achieving an HbA_{1c} <8% was approximately twofold greater with pramlintide (120 μg BID) than with placebo (46 vs. 28%, $P < 0.05$). The glycemic improvement with pramlintide 120 μg BID was accompanied by a mean weight loss (−1.4 kg vs. +0.7 kg with placebo at week 52, $P < 0.05$) and occurred without an overall increase in the severe hypoglycemia event rate. The most common adverse event associated with pramlintide use was transient, mild-to-moderate nausea.

CONCLUSIONS — Mealtime amylin replacement with pramlintide 120 μg BID, as an adjunct to insulin therapy, improves long-term glycemic and weight control in patients with type 2 diabetes.

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Abbreviations: ADA, American Diabetes Association; BID, twice a day; TID, three times a day; ITT, intent-to-treat; LOCF, last observation carried forward; UKPDS, U.K. Prospective Diabetes Study.

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

Type 2 diabetes is increasing in the U.S. and represents a major burden for both affected individuals and the health care system. The U.K. Prospective Diabetes Study (UKPDS) showed that an improvement of glycemic control, as evidenced by a reduction in HbA_{1c} values, reduces the risk of microvascular and possibly macrovascular complications in patients with type 2 diabetes (1). The absence of a discernible threshold effect in that study indicates that any reduction in HbA_{1c} conveys clinical benefit (1). The UKPDS also showed type 2 diabetes to be a progressive disease associated with a gradual loss of β-cell function regardless of therapy (2). As a result, the majority of patients went on to multiple therapies and many advanced to a stage requiring exogenous insulin replacement (1,2).

Despite important advances in insulin therapy, most insulin-treated patients with type 2 diabetes are unable to achieve satisfactory glycemic control (3). Among the barriers to achieving satisfactory glycemic control with insulin in patients with type 2 diabetes are excessive weight gain (1,4–6), failure to adequately control postprandial glycemic excursions (7,8), and an increased risk of hypoglycemia (1,9–11).

Amylin is a pancreatic islet hormone that is normally colocalized with insulin in the β-cells and is cosecreted with insulin in response to meals (12–15). Consequently, β-cell dysfunction in insulin-requiring patients with type 2 diabetes manifests with a markedly impaired postprandial insulin and amylin response (13–16).

Preclinical studies indicate that amylin acts as a neuroendocrine hormone that, after release from pancreatic β-cells, binds with high affinity to specific amylin receptors in selected regions of the brain, including the area postrema where it elicits visceral effects via the vagus nerve

(13,17). Amylin complements the effects of insulin in mealtime glucose regulation via several effects that collectively regulate the rate of postprandial glucose inflow into the circulation, thereby better matching the rate of insulin-stimulated glucose disposal (13–15). These effects include a suppression of nutrient-stimulated glucagon secretion (18) and a slowing of gastric emptying (19).

Clinical studies in insulin-treated patients with type 2 diabetes showed that mealtime subcutaneous injection of pramlintide, a synthetic, equipotent, and soluble peptide analog of human amylin, reduced postprandial hyperglucagonemia (20), slowed the rate of gastric emptying (21), and consequently, improved postprandial glucose excursions in this patient population (13–15,22,23).

The aim of the present study was to determine the long-term efficacy and safety of pramlintide as an adjunct to insulin therapy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population

All 656 patients in this study were ≥18 years of age and had type 2 diabetes requiring insulin treatment for at least 6 months before study initiation. Enrollment criteria included baseline HbA_{1c} ≥8%, absence of severe hypoglycemic or hyperglycemic symptoms for at least 2 weeks before screening, stable body weight (±5 kg), and stable daily insulin dose (±10%) for at least 2 months before the study. Patients using stable doses of metformin or sulfonylureas with their insulin for at least 3 months were included and instructed to maintain their usual oral treatment regimens during the study. Females were postmenopausal, surgically sterile, or using adequate contraception. Exclusion criteria included history of diabetic ketoacidosis consistent with type 1 diabetes; history of clinically significant cardiovascular, pulmonary, central nervous system, gastrointestinal (including gastroparesis), renal, or hematologic diseases; eating disorders (e.g., bulimia or anorexia nervosa); alcohol or drug abuse; acute illness (temperature ≥37.8°C) within 2 weeks before screening; and chronic use of systemic corticosteroids, dexfenfluramine, drugs that affect gastrointestinal motility (e.g., cisapride, metoclopramide), and bile acid–sequestering agents.

The institutional review board of each study site approved the study protocol, and all patients provided written informed consent.

Study design

This was a 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study that began with a 28-day placebo lead-in period during which all patients received subcutaneous injections of placebo TID, given 15 min before major meals (breakfast, lunch, and dinner), in addition to their usual insulin regimen. Patients were then randomized to receive mealtime subcutaneous injections of placebo TID or pramlintide at 90 μg BID, 120 μg BID, or 60 μg TID, again given 15 min before major meals (breakfast, lunch, and dinner). For those patients on BID regimens (breakfast and dinner), placebo was given as a third dose (at lunch) to maintain the blind. Insulin was administered according to the patients preexisting, individual regimen (Table 1). To minimize the confounding effect of concomitant insulin use on glycemic control, patients were encouraged to maintain their existing insulin and/or oral antihyperglycemic regimen and to remain on their usual diet and exercise routine during the course of the study. Regular assessments during the study visits revealed that concomitant treatments did in fact remain largely stable (Table 1). Patients were instructed to not mix insulin and study medication in the same syringe and to inject the two medications at different sites (rotating between abdomen and thighs).

All patients were provided with a One Touch Profile memory glucose meter (Lifescan, Milpitas, CA), along with strips for self-monitoring of blood glucose concentrations, and were instructed to record the glucose readings and insulin doses in diaries. Hematologic and laboratory parameters, HbA_{1c}, lipoprotein values, vital signs, and body weight were monitored throughout the study. Patients also monitored symptoms of hypoglycemia and, if possible, obtained glucose readings when hypoglycemic symptoms occurred.

During the course of the study, results from another study became available which indicated that the 60 μg TID pramlintide dose was less effective compared with higher doses. Consequently, the statistical analysis plan was amended to exclude the 60 μg TID treatment group from formal efficacy analyses and, therefore, data from this group are not presented. The 60 μg TID treatment group (158 randomized patients) remained active in the study, however, such that the study conduct was not affected by the decision.

Efficacy

The primary efficacy end point was the absolute change from baseline in HbA_{1c} at week 26. Secondary efficacy end points included the absolute changes in HbA_{1c} at other time points, changes in body weight from baseline to weeks 26 and 52, and the percentage of patients who achieved American Diabetes Association (ADA) recommended glucose control targets of HbA_{1c} <7 or <8%, respectively (24).

Safety

Safety evaluations included physical examinations, monitoring of adverse events, laboratory parameters, vital signs, and electrocardiograms. In accordance with the Diabetes Control and Complications Trial (DCCT) (25), severe hypoglycemia was defined as an event requiring the assistance of another individual or the administration of glucagon or intravenous glucose and was expressed as event rate per patient year of exposure, thus accounting for multiple events in the same patient and for differences in time of exposure to study medication. The severity of all other adverse events was assessed by the investigators, based on standardized, uniform guidelines (mild: did not interfere with daily activities and required no special treatment; moderate: may have interfered with daily activities but caused only a low degree of inconvenience or concern; severe: interrupted a patient's usual daily activities and required treatment).

Statistical analysis

All efficacy and safety analyses were performed on the intent-to-treat (ITT) population using the last observation carried forward (LOCF) method for most analyses. Two-way ANOVA models with treatment and study site were used to determine statistical significance in mean change from baseline in HbA_{1c} and body weight at weeks 26 and 52. Fisher's protected testing procedure was used to control type 1 errors arising from multiple pair-

Table 1—*Baseline demographics*

	Placebo TID	Pramlintide 90 μg BID	Pramlintide 120 μg BID
n (ITT)	161	171	166
Sex (% M/F)	52/48	49/51	48/52
Age (years)	56.4 ± 10.2	57.0 ± 10.2	56.9 ± 10.5
Race (%)			
White	75	77	73
Black	12	14	13
Hispanic	12	8	13
Other	1	1	1
Body weight (kg)*	96.8 ± 20.5	97.1 ± 19.3	96.7 ± 23.2
BMI (kg/m^2)	33.7 ± 7.2	33.8 ± 6.3	34.1 ± 7.5
Diabetes duration (years)*	12.4 ± 7.0	12.0 ± 6.6	12.1 ± 7.3
HbA_{1c} (%)*	9.3 ± 1.3	9.1 ± 1.1	9.0 ± 1.1

Concomittant therapies	Week 0	Week 52	Week 0	Week 52	Week 0	Week 52
Total daily insulin dose (units)*	74	76	70	72	69	70
Type of insulin used (%)†						
Short-acting only	0	0	1	2	1	0
Long-acting only	14	15	21	19	17	18
Short- and long-acting	86	85	78	79	82	82
Injections/day (%)†						
1 injection	9	5	7	6	9	8
2 injections	68	73	73	72	72	70
3+ injections	23	22	20	22	19	22
Oral anti-hyperglycemic agents, (%)†	27	27	26	23	23	21
Metformin only	14	14	13	13	9	9
Sulfonylureas only	10	12	7	9	9	10
Metformin and sulfonylureas	2	2	6	5	5	5

*Values are mean ± standard deviation; †proportion of subjects

wise comparisons. If the overall ANOVA test was significant at 0.05; then, each pramlintide treatment was compared separately to placebo using Fisher's least significant difference (LSD) method. The sample size ensured at least 90% power to detect at least one significant pramlintide treatment group at the 0.05 significance level using Fisher's protected testing procedure.

RESULTS

Patient disposition and baseline demographics

The study population encompassed a wide range of age, race, body weight, diabetes duration, and entry HbA_{1c} values. All treatment groups were well balanced with respect to baseline demographics and concomitant therapies (Table 1). Preexisting insulin therapy included a wide spectrum of regimens, both in terms of the types of insulin formulations used and the number of daily injections (Table 1). The vast majority of patients was overweight or obese and used a combination of short- and long-acting insulin given either BID or TID. Approximately 25% of patients used metformin and/or sulfonylureas in addition to their insulin (Table 1).

Of the 656 patients randomized (ITT population), 161, 171, and 166 were assigned to the placebo TID, pramlintide 90 μg BID, and pramlintide 120 μg BID groups, respectively (Table 1). Of those, 113 (70%), 122 (71%), and 113 (68%) completed 52 weeks of treatment. Thus, the overall withdrawal rates were comparable across treatment groups (30, 29, and 32% for the placebo TID, pramlintide 90 μg BID, and pramlintide 120 μg BID groups, respectively). The most common reasons for withdrawal were withdrawal of consent and adverse events.

HbA_{1c}

Treatment with pramlintide 120 μg BID led to a sustained reduction from baseline in HbA_{1c} (−0.68 and −0.62% at weeks 26 and 52, respectively) that was significantly greater than that in the placebo group ($P < 0.05$, Fig. 1*A*). Treatment with pramlintide 90 μg BID led to a reduction from baseline in HbA_{1c} (−0.54 and −0.35% at weeks 26 and 52, respectively) that was not significantly different from placebo (Fig. 1*A*). Similar HbA_{1c} reductions to those observed in the ITT population were seen in the evaluable population (change from baseline to weeks 26 and 52: −0.57 and −0.37% for the 90 μg BID group and −0.73 and −0.68% for the 120 μg BID group, respectively).

In the patients receiving pramlintide in addition to their insulin, up to a threefold greater proportion achieved an HbA_{1c} <7% (90 μg BID group 9.4% and 120 μg BID 12.2% vs. placebo group 4.1%) and an almost twofold greater proportion achieved an HbA_{1c} <8% (90 μg BID group 42.4% and 120 μg BID 45.7% vs. placebo group 27.6%) compared with

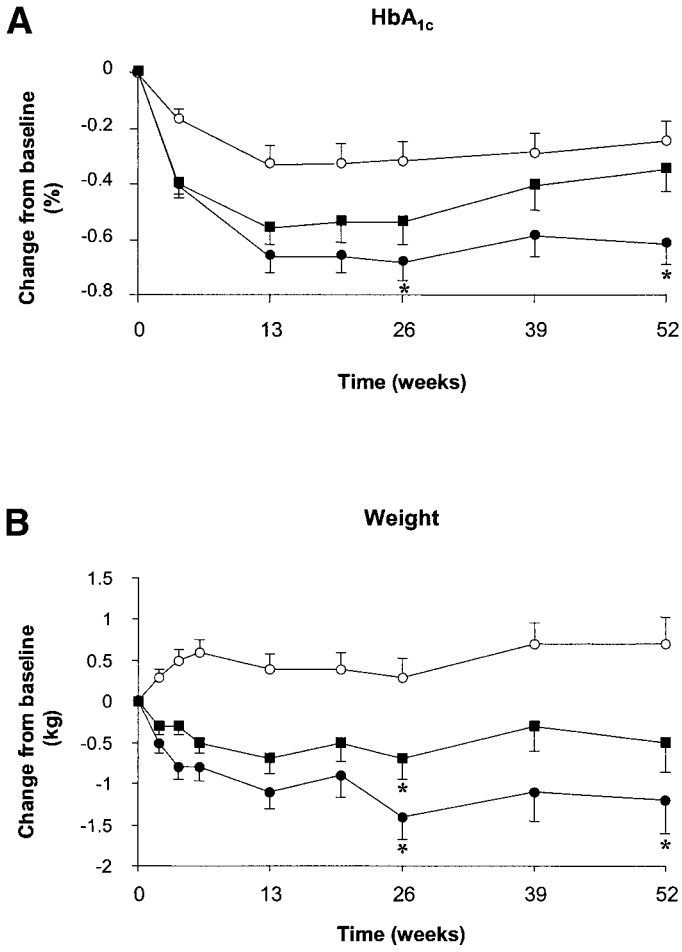

Figure 1—*Change from baseline in mean HbA_{1c} (A) and weight (B) (ITT population). *P < 0.05 for treatment arm versus placebo. ○, placebo; ■, 90 μg BID; ●, 120 μg.*

the patients receiving placebo plus insulin.

Body weight

The greater reduction of HbA_{1c} observed with pramlintide was not accompanied by an increase in body weight (Fig. 1*B*). Instead, patients in both pramlintide treatment groups experienced a reduction in body weight that was significantly different from placebo at week 26 (both $P < 0.05$, Fig. 1*B*). In the 120 μg BID treatment group, the reduction in body weight was sustained to week 52 ($P < 0.05$ vs. placebo), whereas in the 90 μg BID treatment group, the placebo-corrected treatment difference was no longer significant (Fig. 1*B*). Weight reductions similar to those observed in the ITT population were seen in the evaluable population (change from baseline to weeks 26 and 52: −0.7 and −0.5 kg in the 90 μg BID and −1.1 and −1.4 kg in the 120 μg BID groups, respectively).

Stratification of the study population into patients who experienced nausea at any time during the study and those who never reported any nausea revealed that the weight loss observed with pramlintide was not attributable to nausea (placebo-corrected reduction in body weight from baseline to week 52 in the 90 and 120 μg pramlintide groups: −1.1 and −1.5 kg for patients who never experienced nausea and −0.3 and –2.0 kg for patients who experienced nausea).

Stratification of the study population into patients who lost weight during the study and those who gained weight revealed that the reduction in HbA_{1c} observed with pramlintide was not simply a consequence of weight loss (placebo-corrected reduction in HbA_{1c} from baseline to week 52 in the 90 μg pramlintide and 120 μg pramlintide groups: −0.22 and −0.58% for patients who lost weight and –0.29 and −0.53% for patients who gained weight).

Concomitant medications

The greater reduction in HbA_{1c} with pramlintide was not attributable to changes in concomitant treatment with insulin and/or oral hypoglycemic agents. As intended in the protocol, both insulin regimens and oral hypoglycemic regimens remained virtually constant throughout the study in all treatment groups (Table 1).

Safety

There was no evidence of cardiovascular, pulmonary, hepatic, or renal toxicity or of drug-related idiosyncratic side effects associated with pramlintide therapy. No changes in laboratory safety parameters or electrocardiogram variables were observed. There were no differences in fasting lipids, heart rate, or systolic or diastolic blood pressure between the placebo and pramlintide treatment groups.

Nausea and headache were the only treatment-emergent adverse events that occurred with an incidence ≥10% and that were at least two times greater in one of the pramlintide-treatment groups compared with the placebo group (Table 2). These adverse events did not appear to be dose-related and were almost exclusively of mild-to-moderate intensity. The increased incidence of nausea in pramlintide-treated patients, as compared with place bo-treated patients, was transient, i.e., confined to the first 4 weeks of therapy (Table 2). The incidence of nausea in patients concomitantly treated with metformin (19, 35, and 22% for the placebo TID, pramlintide 90 μg BID, and pramlintide 120 μg BID groups, respectively) was roughly similar to that in the overall study population (Table 2).

The greater reductions in HbA_{1c} in the pramlintide treatment groups were not associated with an overall increase in severe hypoglycemia (Table 2). During the first 4 weeks, the severe hypoglycemia event rate was increased in the pramlintide 120 μg BID group, but not in the pramlintide 90 μg BID group, compared with the placebo group. Beyond the first 4 weeks of treatment, the severe hypoglycemia event rates in both pramlintide treatment groups were comparable to placebo and were lower in the second half of the study, despite the greater reduction in HbA_{1c}.

CONCLUSIONS

Patients with type 2 diabetes who are no longer adequately controlled with oral

Table 2—*Incidence of severe hypoglycemia and treatment-emergent adverse events with an incidence ≥10% and the incidence in one of the pramlintide groups at least double that of the placebo group (ITT population)*

	Placebo TID	Pramlintide 90 μg BID	Pramlintide 120 μg BID
Severe hypoglycemia*			
0–52 weeks	0.3 ± 0.05	0.1 ± 0.03	0.3 ± 0.05
0–4 weeks	0.3 ± 0.20	0.1 ± 0.08	0.9 ± 0.30
4–26 weeks	0.3 ± 0.07	0.2 ± 0.06	0.4 ± 0.09
26–52 weeks	0.2 ± 0.06	0.0 ± 0.02	0.1 ± 0.05
Nausea (%)†			
0–52 weeks	14 (1)	31 (4)	30 (2)
0–4 weeks	3 (0)	18 (2)	16 (2)
4–26 weeks	5 (1)	5 (2)	8 (0)
26–52 weeks	4 (0)	3 (0)	3 (0)
Headache (%)†	8 (0)	15 (1)	17 (1)

*Event rate per patient year (total number of events for all patients in a given treatment regimen/total number of patient years of observation for all patients in that treatment regimen). Values are mean ± standard deviation. †Non-severe (severe) as defined in RESEARCH DESIGN AND METHODS.

hypoglycemic agents manifest both insulin and amylin deficiencies at mealtime (13–16). Insulin replacement therapy, despite being the most powerful glucose-lowering treatment currently available, does not lead to satisfactory glycemic control in the majority of patients (3) and is associated with an increased risk of hypoglycemia (1,9–11) and excessive weight gain (4–6). The present study indicates that addition of pramlintide to the existing insulin therapy of patients with type 2 diabetes leads to an improvement of long-term glycemic control and an increased proportion of patients attaining glycemic targets beyond that obtained with insulin therapy alone. Importantly, this glycemic improvement occurred without weight gain and without an increased overall rate of severe hypoglycemia.

Previous clinical studies in patients with type 2 diabetes have shown that the addition of pramlintide to mealtime insulin injections reduces postprandial glycemic excursions (13–15,22,23). This is achieved via effects that are complementary to those of insulin: a correction of postprandial hyperglucagonemia (20) and a slowing of gastric emptying (21). The present study indicates that the postprandial glucose-lowering properties of pramlintide can translate into improved long-term overall glycemic control, as evidenced not only by a significant and sustained reduction of HbA_{1c}, but also by a substantial increase in the proportion of patients achieving an HbA_{1c} of <7 and <8%, the glycemic targets recommended by the ADA (24). While there was heterogeneity in the HbA_{1c} response to the different pramlintide dosing regimens, the most robust and significant response was seen in the pramlintide 120 μg BID group. This is consistent with results from another long-term, randomized, placebo-controlled trial in patients with type 2 diabetes in which a pramlintide dose of 150 μg TID was found to be the most effective dose (26). These findings indicate that 120 μg BID is a safe and efficacious pramlintide dose regimen for patients with type 2 diabetes. When interpreting the magnitude of the HbA_{1c} reductions in the pramlintide treatment groups, several aspects should be considered. First, although not measured as end points in the present long-term study, previous short-term studies indicate that pramlintide's glucose-lowering effects are confined to the postprandial period with no effect on fasting glycemia. Second, it is important to recognize that the study used an add-on design, i.e., pramlintide was added as an adjunct to the preexisting treatment with insulin, used either alone or in combination with metformin and/or sulfonylureas. Because these concomitant therapies remained constant over the course of the study, it can be concluded that the addition of pramlintide results in a further glycemic improvement above and beyond that achieved with these preexisting therapies. This is consistent with pramlintide reducing postprandial glucose excursions via a unique and novel mechanism of action (13–15).

The study population included a wide range of ages, diabetes durations, and entry HbA_{1c} values. Subjects were, on average, representative of insulin-treated patients with type 2 diabetes in the U.S., where the mean HbA_{1c} is ~9% and the mean BMI is well above 30 kg/m^2 (3). This patient population has limited therapeutic options with respect to adjunctive therapies. In the present study, ~15% of the patients used metformin and ~10% used sulfonylureas as an adjunct to insulin. Subgroup analyses revealed that pramlintide was as effective in these patients as it was in patients treated with insulin alone (data not shown). Moreover, in multivariate analyses, assignment to study drug was found to be the only factor that determined the change in HbA_{1c}, indicating that pramlintide improved glycemic control in this population regardless of age, sex, race, body weight, diabetes duration, and preexisting antihyperglycemic therapy.

A major challenge in the pharmacological management of type 2 diabetes is that treatment with insulin and most oral hypoglycemic agents, with the exception of metformin (27,28), is frequently accompanied by excess weight gain in this predominantly obese patient population. In the present study, the improvement in glycemic control with pramlintide was associated with significant weight loss. The mechanism underlying the observed weight effect of pramlintide has not yet been systematically studied in humans. However, there is increasing evidence from rodent studies implicating amylin as a centrally acting postprandial satiety signal (29,30). In those studies, amylin dose dependently reduced meal size and overall food intake (29), whereas administration of a selective amylin antagonist increased feeding and body fat stores (30).

Unlike antiobesity agents, which may improve glycemic control as the result of a reduction in body weight (31,32), pramlintide's effects to simultaneously improve glycemic and weight control in patients with type 2 diabetes appear to occur via two independent mechanisms. This is supported by previous studies in which pramlintide selectively reduced postprandial but not fasting glucose concentrations (22,23) and by the finding in the current study that HbA_{1c} was reduced regardless of whether patients gained or lost weight. It is also noteworthy that the

observed weight reduction with pramlintide therapy occurred in patients who had been on established insulin therapy and who had been advised to not change their diet and exercise regimen during the study. Further studies are therefore warranted to examine the weight effect of pramlintide when used in conjunction with behavioral modification, as well as during the initiation of insulin therapy, when weight gain is typically most pronounced (4–6).

Another important finding was that the improvement in glycemic control with pramlintide was not associated with an increased overall event rate of severe hypoglycemia. Although severe hypoglycemia is generally less common in type 2 than in type 1 diabetes, the risk increases with increasing type 2 diabetes duration and is typically further enhanced when glycemic control is improved with insulin therapy alone, a problem of particular concern in elderly patients (9–11).

Pramlintide therapy was generally safe and well tolerated. There was no evidence of toxicity to any of the major organ systems, and the overall incidence of severe adverse events was similar in the pramlintide and placebo groups. The only treatment-emergent adverse events that occurred with an incidence ≥10% in any treatment group and that were at least two times greater in pramlintide-treated patients were nausea and headache (Table 2). As in previous long-term studies in patients with type 1 and type 2 diabetes (26,33–35), nausea was usually mild to moderate in severity and transient in duration. The majority of pramlintide-treated patients (~70%) did not experience nausea during the study and only 2–4% experienced nausea of more severe intensity (Table 2). While the incidence of headache appeared to be greater in the pramlintide-treated groups compared with the placebo-treated group in the present study, this adverse event was not found to be more frequent with pramlintide treatment in any of the other long-term, placebo-controlled trials in patients with type 1 and type 2 diabetes (26,33, 34).

In conclusion, mealtime amylin replacement with pramlintide as an adjunct to insulin therapy appears to be safe and efficacious in improving long-term overall glycemic and weight control in patients with type 2 diabetes. Importantly, the improvement in glycemic control with pramlintide was accompanied by a mean reduction in body weight and no overall increase in severe hypoglycemia. Because of these unique and desirable clinical benefits, pramlintide may become a valuable addition to the arsenal of therapies available to patients with type 2 diabetes.

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