

Incretin Mimetics

18 Outcomes of Pramlintide Therapy in a Real-World Scenario

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Background: Pramlintide is indicated for patients with diabetes mellitus (DM) who are taking prandial insulin replacement but have not achieved adequate glycemic control.

Objective: To evaluate the effectiveness and safety of pramlintide at an academic DM clinic.

Methods: Subjects who began taking pramlintide ≥ 3 months before data collection were considered for inclusion in this retrospective, observational study. The 46 subjects were 47 ± 16 years old, 65% female, 48% white, and 43% Hispanic; 60% had type 1 DM, and overall duration of DM was 19 ± 11 years.

Results: Compared with baseline, after 3 months of pramlintide therapy there was a statistically significant decrease in mean glycosylated hemoglobin (A1C) level ($8.0 \pm 1.0\%$ vs $7.6 \pm 1.0\%$; $P = 0.03$), an increase in total daily insulin dose (54.7 ± 35.2 vs 60.3 ± 39.8 U; $P = 0.03$), but no significant change in weight (201.6 ± 54.2 vs 199.8 ± 55 lb). The largest decrease from baseline in A1C level occurred in the subset of patients with type 1 DM ($8.1 \pm 1.2\%$ to $7.6 \pm 1.0\%$; $P = 0.006$), while A1C decreased only slightly in patients with type 2 DM ($8.0 \pm 0.7\%$ to $7.8 \pm 0.9\%$). Hypoglycemia was reported in 10 subjects (4 severe episodes). The only predictor of response (A1C decrease of $>1\%$) was baseline A1C level. At 6 months, 55% of subjects had discontinued pramlintide therapy (13% due to cost). Side effects included nausea (55%), fatigue (36%), headache (15.2%), and vomiting (6%).

Conclusion: Pramlintide therapy appears to lower A1C level slightly, with no appreciable weight loss or insulin-dose reduction observed in a real-world scenario. Side effects, particularly gastrointestinal, are common, and discontinuation of therapy is frequent.

19 Effect of Adjunctive Mealtime Pramlintide Therapy on Treatment Satisfaction Mediated Primarily via Attenuation of Postprandial Glucose Excursions

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Background: Responses to a 14-item, study-specific, treatment-satisfaction survey indicated that intensively treated patients with type 1 diabetes mellitus were significantly more satisfied after 29 weeks of double-blind SC pramlintide injections compared with placebo injections.

Objective: To explore whether week-29 changes in glycosylated hemoglobin (A1C) level, weight, insulin use, and average postprandial glucose (AVPPG) contributed to survey outcomes.

Methods: This was a post hoc analysis. Patients randomized to double-blind SC mealtime injections of pramlintide ($n = 130$) or placebo ($n = 136$) for 29 weeks completed a 14-item survey. Mean baseline characteristics, including A1C (8.1%), body mass index (28 kg/m^2), and age (41 years), were similar in the 2 groups. The survey used a 6-point Likert scale and was administered under double-blind conditions. Regression analysis evaluated if week-29 changes in A1C, weight, total daily insulin dose, and AVPPG contributed to group differences on survey outcomes.

Results: Twelve of the 14 survey items favored pramlintide. After week-29 changes in A1C, weight, total daily insulin dose, and AVPPG were taken into account, 6 of the 14 survey items remained significant. Of these, only AVPPG significantly contributed to variation in survey responses, an effect specific for pramlintide-treated patients.

Conclusion: Pramlintide's effect on attenuating postprandial glucose excursions was the primary factor differentiating the 2 groups' survey responses.

20 Pramlintide Reduced Markers of Oxidative Stress in the Postprandial Period in Patients with Type 2 Diabetes Mellitus

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Background: Abnormal postprandial glucose excursions causing oxidative stress in patients with diabetes mellitus (DM) may play a role in the development of vascular pathology.

Objective: To assess the effects of pramlintide on markers of oxidative stress in the postprandial period.

Methods: This was a post hoc analysis. In a randomized, single-blind, placebo-controlled, crossover study, 19 insulin-using subjects with type 2 DM (age, 50 ± 9 years; duration of DM, 15 ± 10 years; glycosylated hemoglobin level, $9.3\% \pm 1.6\%$ [mean \pm SD]) underwent 2 standardized meal tests. In addition to their preprandial insulin lispro injection (17.5 ± 10.8 U and 18.1 ± 11.4 U [mean \pm SD] at $t = 0$ minutes for pramlintide and placebo, respectively), subjects received a subcutaneous injection of pramlintide ($120 \mu\text{g}$ at $t = 0$ minutes) or placebo ($t = -15$ minutes). Plasma glucose concentrations and markers of oxidative stress (nitrotyrosine [NT], oxidized low-density lipoprotein cholesterol [OxLDL-C], and total radical-trapping antioxidant parameter [TRAP]) were assessed at baseline and during the 4-hour postprandial period.

Results: Compared with placebo, pramlintide reduced postprandial excursions of glucose, NT, and OxLDL-C and protected TRAP from consumption (**Table**). Correlation analysis revealed positive associations between placebo-corrected glucose AUC, NT, and OxLDL-C and a negative association between placebo-corrected glucose AUC and TRAP. The most frequent adverse events were mild hypoglycemia and nausea.

Conclusion: Reductions in postprandial glucose excursions achieved by adding pramlintide to a rapid-acting insulin injection in patients with type 2 DM were associated with notable reductions in markers of postprandial oxidative stress.

Table.

Postprandial Excursions (incremental AUC _{0-4h})	Pramlintide (µg)	Placebo	P value*
Glucose, mmol/L · h	+2.0 ± 1.5	+10.4 ± 2.2	0.0007
NT, nmol/L · h	+2.7 ± 1.83	+7.1 ± 2.0	0.0441
OxLDL-C, U/L · h	+6.0 ± 9.1	+18.0 ± 10.3	0.2342
TRAP, µmol/L · h	-18.6 ± 10.5	-59.0 ± 16.3	0.0189

NT = nitrotyrosine; OxLDL-C = oxidized low-density lipoprotein cholesterol; TRAP = total radical-trapping antioxidant parameter.

*Mean ± SE, P values based on mixed-effects models.

21 Pramlintide, as an Adjunct to Basal Insulin, Decreased Glycosylated Hemoglobin Level and Body Weight in Patients with Type 2 Diabetes Mellitus

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Background: Pramlintide, an analogue of the β-cell hormone amylin, is used as an adjunct to mealtime insulin to reduce postprandial glucose concentration, glycosylated hemoglobin (A1C) level, and body weight.

Objective: To assess data from post hoc analyses of 2 subsets of patients with type 2 diabetes mellitus (DM) treated with pramlintide and basal insulin only (plus or minus oral antidiabetic agents).

Methods: One patient cohort (pramlintide: n = 18; age, 59 ± 11 years; A1C level, 9.4 ± 1.3%; weight, 88.4 ± 16.5 kg; body mass index [BMI], 31.8 ± 6.1 kg/m²; placebo: n = 11; age, 56 ± 9 years; A1C level, 9.4 ± 1.6%; weight, 92.0 ± 13.4 kg; BMI, 31.2 ± 5.1 kg/m²; mean ± SD) was from a double-blind, placebo-controlled, 52-week study. The second patient cohort was from a 52-week, multicenter, open-label study of 10 patients (age, 60 ± 12 years; A1C level, 8.1 ± 1.3%; weight, 109.2 ± 26.6 kg; BMI, 35.7 ± 8.1 kg/m²; mean ± SD). Endpoints were change in A1C, body weight and insulin dose, and adverse events.

Results: In the placebo-controlled study, pramlintide treatment (120 µg BID), as an adjunct to basal insulin (neutral protamine Hagedorn, lente, ultralente), reduced A1C level (pramlintide: -1.2 ± 0.2% vs placebo: -0.5 ± 0.2%; P < 0.05) and body weight (pramlintide: -2.3 ± 1.0 kg; placebo: -0.9 ± 1.0 kg; mean ± SE). Similarly, in the open-label study, pramlintide (120 µg BID/TID before major meals), as an adjunct to insulin glargine, reduced A1C level (-0.8 ± 0.3% [95% CI = -1.40, -0.22]) and body weight (-2.8 ± 1.03 kg [95% CI = -5.12, -0.47]; mean ± SE, baseline corrected) despite an 18 ± 10% decrease in basal insulin dose. In both studies, pramlintide was generally well tolerated. Common adverse events included nausea, vomiting, dyspepsia, and abdominal pain. No episodes of severe hypoglycemia occurred in pramlintide-treated patients from either cohort.

Conclusions: The improved glycemic control and decreased body weight seen in these limited analyses warrant further clinical investigation of pramlintide in patients with type 2 DM who are not achieving optimal glycemic control with basal insulin.