Considering Pramlintide Therapy for Postprandial Blood Glucose Control

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Abstract

Diabetes is a chronic disease affecting > 20 million Americans, and its incidence, especially in the form of type 2 diabetes, is increasing. Multiple therapeutics are available that address the dysregulation of the multiple hormones responsible for glucose homeostasis. Despite the various options, tight glycemic control is often elusive. Additionally, the pursuit of tight glycemic control is generally accompanied by various clinical challenges, such as hypoglycemia, weight gain, and glucose fluctuations, in particular, postprandial fluctuations.

Several therapeutic options are currently available to address postprandial glucose fluctuations, including rapid-acting insulin analogs, incretin mimetics, dipeptidyl peptidase IV inhibitors, α-glucosidase inhibitors, meglitinides, and amylinomimetics. This article presents the experiences of three patients for whom pramlintide, an amylinomimetic, was identified as an appropriate therapeutic option. Practical considerations for clinicians, patient lifestyle factors, and perceptions of pramlintide therapy are also presented.

Diabetes, a chronic disease affecting ~ 20.8 million Americans,[1] is characterized by chronic hyperglycemia resulting from the body's inadequate physiological response to glucose. In type 1 diabetes, secretion of insulin and amylin into the circulatory system is absolutely deficient because of the destruction of pancreatic β-cells, whereas in type 2 diabetes, secretion of insulin and amylin is abnormal because of progressive β-cell dysfunction.[2–4] In addition to the physical manifestations of the disease, diabetes also carries the risk for development of microvascular and macrovascular complications.[1,5–9]

Patient concerns extend beyond the threat of diabetes-related complications. Daily life is burdened by high and low glucose concentrations, which require vigilant daily monitoring, and by the fear of hypoglycemia. Management of diet and physical activity to avoid glucose excursions, concerns regarding weight, and a sense of constant hunger add additional stress to the daily diabetes routine, leaving many patients feeling inadequate in the management of their disease. However, with the recent introduction of new classes of therapies that specifically address

postprandial hyperglycemia without causing concomitant weight gain, patients now have additional tools to manage their diabetes.

Glucose Homeostasis

Glucose homeostasis is maintained by a complex multihormonal system that continuously balances the appearance and disappearance of glucose. Key pancreatic and intestinal hormones that regulate this system include glucagon, insulin, amylin, and glucagon-like peptide-1 (GLP-1).[10] Glucagon, secreted from the pancreatic α-cells, regulates glucose appearance by signaling the liver to produce and release glucose in the fasting state.[10] Insulin and amylin are cosecreted from the pancreatic β-cells in response to meals. During the postprandial period, insulin suppresses hepatic glucose production and facilitates the uptake of glucose from the circulation into the peripheral tissues for use as an energy source,[10] thus playing an important role in the disappearance of glucose from the circulation. Amylin influences the rate of glucose appearance into the circulation by three mechanisms: suppression of postprandial glucagon secretion, regulation of gastric

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emptying, and regulation of appetite and food intake.[11] Postprandial glucagon secretion is also suppressed by insulin and GLP-1. GLP-1, secreted by intestinal cells in response to meals, enhances glucose-dependent insulin secretion, suppresses postprandial glucagon secretion, slows gastric emptying, and reduces food intake.[10]

The complementary actions of insulin and amylin help to maintain postprandial glucose homeostasis. In patients with diabetes, the relative or absolute deficiency of insulin and amylin disrupts maintenance of glucose homeostasis. Under the influence of glucagon, hepatic glucose production assures adequate glucose concentrations during the fasting state. In the fed state, hepatic glucose production is not needed. However, in patients with diabetes, glucagon secretion does not decrease appropriately even when meal-derived glucose is present, further exacerbating the meal-derived hyperglycemia typical of diabetes.

Clinical Challenges

Chronic hyperglycemia increases the risk of developing microvascular and macrovascular complications.[5,7,8] Patients with diabetes and their health care providers are encouraged to achieve tight glycemic control to reduce the occurrence of diabetes-related complications. However, pursuit of this goal is often accompanied by the challenges of preventing hypoglycemia, avoiding weight gain associated with treatment of diabetes, and reducing glucose fluctuations, in particular, postprandial fluctuations.

The goal of diabetes therapy is to achieve and maintain near-normal glycemia. However, as patients approach normoglycemia, the risk of severe hypoglycemia increases.[7,12] Hypoglycemia is often a deterrent to intensive therapy for patients and health care providers and is also problematic for patients' significant others. Additionally, insulin and many oral agents used to treat diabetes often result in weight gain,[7,13] which is an independent risk factor for other disorders, such as cardiovascular disease.[14,15]

Hemoglobin A_{1c} (A1C) is the standard indicator of average glycemic control in diabetes. However, even as A1C approaches the target range for patients with diabetes, blood glucose concentrations may not consistently fall into the euglycemic range.[16] The

interactions of exogenously administered insulin, ingested glucose, and hepatic glucose production can cause wide fluctuations in glucose concentrations, resulting in hypoglycemic and hyperglycemic excursions. Lack of glucagon suppression, which results in inappropriate postprandial hepatic glucose production, and accelerated gastric emptying, which contributes to rapid, ill-timed intestinal glucose absorption, are major contributors to postprandial hyperglycemia.[17]

Postprandial Glycemic Control

The American Diabetes Association recommends a target A1C of < 7.0%.[18] A1C is a composite of long-term average fasting and postprandial glucose levels. As A1C levels approach 7.0%, the relative contribution of postprandial glucose to overall glycemic control is ~ 70%.[19] Elevated postprandial glucose concentrations can adversely affect mood and cognitive function.[20,21] Additionally, recent studies have reported that hyperglycemia-induced oxidative stress may increase the risk of cardiovascular disease.[22–26] Thus, attention to postprandial glucose is necessary to achieve glycemic targets and reduce risk of long-term diabetes complications.

A number of therapeutic agents address postprandial glucose control, including rapid-acting insulins, incretin mimetics, dipeptidyl peptidase IV (DPP-IV) inhibitors, α-glucosidase inhibitors, meglitinides, and amylinomimetics. The cases that follow describe the experiences of three patients for whom pramlintide, an amylinomimetic, was identified as an appropriate therapeutic option. Practical considerations for clinicians, patient lifestyle factors, and perceptions of pramlintide therapy are also presented.

Case Studies

The cases presented below are intended to provide practical education based on the actual clinical experience of the authors with pramlintide. Insulin adjustment strategies discussed are based on clinicians' assessments of individual patients and may differ from the pramlintide prescribing information. Individualized patient assessment and clinical judgment are crucial to effective patient care.

Case 1: a patient with type 2 diabetes.

Judy is a 43-year-old woman diagnosed with type 2 diabetes 12 years

ago. She has a history of hypertension, dyslipidemia, and obesity. She is a single mother who works an erratic schedule of day and night shifts as a radiology technician. Initially, Judy was able to control her diabetes with diet and exercise, but after 2 years, other treatment options were needed to maintain glycemic control.

Patients with type 2 diabetes have a broad choice of therapies, including oral medications, such as biguanides, thiazolidinediones, sulfonylureas, meglitinides, and DPP-IV inhibitors, and injectables, such as insulin, amylinomimetics, and incretin mimetics. These medications address glycemic control through several different mechanisms of action (Table 1).The biguanides decrease hepatic glucose production, sulfonylureas and meglitinides promote insulin secretion, and thiazolidinediones improve target cell response to insulin, thereby decreasing hepatic glucose production and increasing glucose uptake.[27] Exenatide, an incretin mimetic, exhibits many of the actions of GLP-1, whereas DPP-IV inhibitors slow the degradation of GLP-1.[28,29] Pramlintide, a soluble amylin agonist, exhibits glucoregulatory actions similar to those of amylin.[30–34]

When diet and exercise were no longer effective, metformin, a biguanide, was added to Judy's treatment regimen. Over the next few years, metformin alone was insufficient in maintaining glycemic control, and nateglinide, a meglitinide, was added. Eventually, the combination of metformin and nateglinide no longer provided adequate glycemic control, and basal insulin was added.

Patients with type 2 diabetes are often reluctant to start insulin therapy, despite its glycemic benefits. Because of the increased risk of hypoglycemia, insulin therapy requires more vigilant blood glucose monitoring and active dosage adjustments based on food intake and exercise. Because insulin carries the potential for hypoglycemia and weight gain,[7,13] patients with type 2 diabetes often view insulin as a treatment of last resort and as an indication of their failure to manage their diabetes.[35]

Ongoing evaluation of glycemic control revealed the need to further modify Judy's treatment regimen. One year after the addition of basal insulin, nateglinide treatment was discontinued, and premeal insulin was

Table 1. Therapies for Patients With Type 2 Diabetes[11,27–29]

Therapy		Glucose uptake	Insulin secretion	Insulin sensitivity	Delay glucose absorption	Hepatic glucose production	Delay gastric emptying	Food intake	Side effects
Oral Medications:									
Insulin secretogogues	Type 2		•			•			Hypoglycemia, weight gain
Biguanides	Type 2			•		•			Diarrhea, nausea, vomiting, bloating
α-Glucosidase inhibitors	Type 2				•				Diarrhea, flatulence
Thiazolidinediones	Type 2			•		•			Weight gain, edema
DPP-IV inhibitors	Type 2		•			•			Headache, nasopharyngitis, mild hypoglycemia
Injectables:									
Insulin	Type 2/1	•				•			Hypoglycemia, weight gain, edema
Amylinomimetics (pramlintide)	Type 2/1					•	•	•	Nausea, insulin-induced severe hypoglycemia
Incretin mimetics (exenatide)	Type 2		•			•	•	•	Nausea, sulfonylurea-induced hypoglycemia

Table 2. Suggested Pramlintide Titration Dosing Schedule*

Days	Type 2 diabetes (µg)	Type 1 diabetes (µg)
1	60 (Reduce insulin by 50%)	15 (Reduce insulin by 50%)
4	120	30
7	120	45
10	120	60

Dose increases should be individualized and primarily based on the absence of clinically significant nausea for at least 3 days.

added. Judy then began continuous subcutaneous insulin infusion (insulin pump therapy) with insulin aspart. Subsequently, she gained 14 lb, and evidence of increased insulin resistance emerged. Pioglitazone was then added, and her weight gain continued. Because control of blood glucose concentrations, particularly during the postprandial period, remained problematic and weight was a continuing challenge, pramlintide was recommended.[16,36–40] Injection of pramlintide acetate, a soluble amylin agonist, is indicated as an adjunct treatment to mealtime insulin in patients with type 1 or type 2 diabetes who are not

achieving optimal glycemic control.

Judy was instructed to initiate pramlintide before meals at a dose of 60 µg (10 units in a U-100 insulin syringe) (Table 2). On initiation of pramlintide, her mealtime insulin boluses were decreased by 50%, and she was advised to initially increase self-monitoring of blood glucose (SMBG) to 6–8 times a day to evaluate postprandial glycemia and be mindful of trends that might predict hypoglycemia. Based on SMBG results, she was advised to adjust her insulin to address the hyperglycemia that resulted from the initial reduction of insulin. With increased SMBG and

active adjustment of insulin based on glucose results, Judy and her health care provider were able to effectively deal with the postprandial hyperglycemia that initially occurred during the pramlintide titration period.

In clinical trials of pramlintide, the most common treatment-emergent adverse event observed was mild to moderate nausea.[41–44] In addition, insulin-induced severe hypoglycemia occurred more frequently in pramlintide- than in placebo-treated patients, particularly in those with type 1 diabetes. Nausea and hypoglycemia were more prevalent in early clinical trials that used fixed insulin and pramlintide doses during the initiation period. In subsequent trials, in which pramlintide was initiated by dose titration, and insulin doses were proactively reduced, the incidence of nausea and hypoglycemia was reduced.[45,46]

Initially, Judy experienced fatigue, dry mouth, and a loss of appetite, which she perceived as nausea. These symptoms subsided after 2 weeks on pramlintide, and the doses of pramlintide were increased to the target dose for patients with type 2 diabetes (120 µg, or 20 units). Additionally,

she began using the dual wave feature of her pump for bolus delivery to more effectively achieve stable glucose concentrations after meals.

Judy's current diabetes regimen includes insulin aspart delivered by an insulin pump, metformin (1,000 mg twice daily), and pramlintide (120 µg, or 20 units) with meals containing at least 30 g of carbohydrate and/or 250 kcal. Judy has returned to testing her blood glucose four times a day with additional periodic postprandial glucose checks. Other concomitant medications include quinapril, metoprolol, furosemide, and ezetimibe/simvastatin.

After 12 weeks of treatment, Judy experienced reductions in A1C from 8.1 to 7.1%, in daily insulin requirements from 85 to 60 units/day, and in weight from 229 to 214 lb. She reported feeling "better than I have felt in a long time." Subsequent to these improvements, Judy began to engage in other behavioral lifestyle changes.

Practical considerations
- Initiate pramlintide treatment based on type of diabetes, and advance the dose based on patient tolerability. If nausea is experienced, consider the following:
  ⇒ Assess the timing of meals relative to pramlintide administration,
  ⇒ Educate patients to recognize that pramlintide may cause early satiety or a sense of fullness, and
  ⇒ Inform patients that they may become uncomfortable or experience nausea if eating continues past the sensation of fullness.
- Reduce premeal insulin by 50% on initiation of pramlintide; subsequently modify the insulin dosage based on the patient's individual glycemic response.
- Further modifications in insulin doses and/or timing may be necessary to safely achieve maximal effects.
- The psychological benefits that accompany successes in diabetes management (self-confidence, empowerment, and self-efficacy) may promote additional positive behavioral changes.[47,48]

Case 2: a patient with type 1 diabetes.
Lacy is a 51-year-old woman who was diagnosed with type 1 diabetes 43 years ago and now also has nonproliferative retinopathy. She is physically active and works irregular hours as a medical office receptionist. Using a multiple daily insulin dose regimen with ultralente (purchased in bulk before its removal from the market) and lispro, Lacy maintained an A1C at < 6.5% for 18–20 years. Recently, she has noticed wide fluctuations in blood glucose concentrations with frequent mild to moderate hypoglycemia, despite her favorable A1C.

Insulin, the first hormone discovered to regulate glucose homeostasis, has been the primary diabetes therapeutic agent since the early 20th century. In type 1 diabetes, the destruction of pancreatic β-cells results in both insulin and amylin deficiencies.[11] With the development of pramlintide, patients with type 1 diabetes now have an adjunct treatment to mealtime insulin. During clinical trials, patients with type 1 diabetes using mealtime insulin and treated with 30 or 60 µg (5 or 10 units) of pramlintide three to four times daily achieved reductions in A1C accompanied by sustained reductions in body weight through week 26.[43,44] Pramlintide treatment reduced glucose excursions and postprandial hyperglycemia.[16,36–40]

Hoping to better control postprandial hyperglycemia, Lacy and her health care provider opted to try pramlintide, the only other therapeutic option available for patients with type 1 diabetes. Pramlintide was initiated at 15 µg (2.5 units) three times daily and titrated by 15 µg (2.5 units) every 3–7 days based on tolerability (Table 2), until the target dose of 60 µg (10 units) three times daily was achieved. Under the guidance of her health care provider, Lacy increased her glucose monitoring and reduced her prandial insulin dose by ~ 30%. The initial premeal insulin reduction was made after careful consideration of Lacy's overall level of glycemic control, as measured by A1C, and review of her previous 3 weeks of SMBG data.

Lacy experienced satiety with pramlintide treatment and also mild hypoglycemia if she took her indicated insulin dose and ate less food than expected. Consequently, she administered her pramlintide with her first bite of food and her mealtime insulin halfway through the meal based on her actual food intake. When she became accustomed to pramlintide and could predict her meal size, she resumed preprandial dosing of her mealtime insulin.

Lacy's current diabetes regimen includes insulin lispro with breakfast, lunch, and dinner; ultralente insulin twice daily; and pramlintide (60 µg, or 10 units) with meals containing at least 30 g of carbohydrate and/or 250 kcal.

Lacy has experienced a reduction in postprandial hyperglycemia, infrequent episodes of mild to moderate hypoglycemia related to reduced food intake, and an overall smoothing of blood glucose control. Despite having an A1C and weight within target range before pramlintide therapy, her A1C decreased further, from 6.4 to 5.9%, and her weight increased from 146 to 147 lb after 18 months on pramlintide therapy. Lacy has not experienced nausea except when overeating. She reported having more energy and feeling more rested when she arose in the morning. Lacy does not have medical insurance but has elected to pay out of pocket to facilitate continued use of pramlintide.

Practical considerations
- Individualize insulin doses and timing adjustments based on patients' eating habits.
- A1C is a reflection of overall glycemic control; reducing glucose excursions can contribute to improvement in A1C.
- Improvement in glycemic control was associated with perceived improvements in general health, sleep, and energy.[49]

Case 3: a patient with type 2 diabetes.
Joe is a 62-year-old man diagnosed with type 2 diabetes in 1992. He has a history of obesity (BMI = 43 kg/m²), hypertension, and hypercholesterolemia treated with lisinopril and atorvastatin. When initial treatment with diet and exercise were unsuccessful in controlling blood glucose levels, a sulfonylurea was started. Blood glucose concentrations were initially controlled with a sulfonylurea, but after several years, glucose control deteriorated, and metformin was added. Glycemic improvement on this two-drug regimen lasted for a little over 1 year. When a thiazolidinedione was added, the modest improvement in glycemia was offset by progressive weight gain.

Joe's mother died of renal failure resulting from long-standing, poorly controlled diabetes, so Joe was very amenable to starting insulin when

glycemic goals were still not achieved. He learned carbohydrate counting and started insulin glargine for basal coverage and insulin aspart to cover his meals. Using this regimen, his A1C dropped to 7.4%, and fasting blood glucose concentrations were uniformly < 140 mg/dl. However, with improved glucose control, Joe steadily gained weight, and his BMI increased to ~ 45 kg/m².

In an effort to improve his glycemic and weight control, pramlintide therapy with meals was initiated. Pramlintide was started at 60 µg (10 units), and his mealtime aspart doses were decreased by 50%. Once Joe reached the target pramlintide dose (120 µg, or 20 units) for patients with type 2 diabetes, he worked with his health care provider to adjust his insulin dosage to optimize glycemic control. He lost 10 lb during the first month of pramlintide therapy. By the third month, his weight loss was 15 lb, and his A1C had dropped from 7.3 to 7.1%. Over the next several weeks, his blood glucose concentrations steadily rose, and his A1C eventually returned to baseline. Joe reported that the initial improvement in glucose concentrations and weight loss excited him, but he admitted to getting tired of the extra injections. He frequently missed at least one dose of pramlintide each day, generally before lunch. He also skipped pramlintide doses so he could consume his pre-pramlintide amounts of pizza and beer with his friends without feeling so full. He continued to use pramlintide for 16 months, but his weight and glycemic control did not show further improvement.

Joe experienced early success with pramlintide. However, when use of pramlintide interfered with his desire to continue previous eating behaviors, he used pramlintide only sporadically. Joe may have been contemplating change but either was not prepared for it or lacked a supportive environment sufficient to sustain a change in his lifestyle.

Practical considerations
- When using pramlintide, other diabetes care strategies should not be neglected. Nutrition and physical activity continue to be important.
- Regular dosing of pramlintide is important. Intermittent dosing may adversely affect the potential for improvement in blood glucose control, satiety, and weight control.

- Appropriate patient selection is important to successful use of pramlintide.
- Understanding patients' desires to change behavioral aspects of self-care may help determine the most effective therapeutic options for each patient.

Clinical Use
Pramlintide is indicated for patients with type 1 or type 2 diabetes who use mealtime insulin therapy (with or without a concurrent sulfonylurea agent and/or metformin for patients with type 2 diabetes) and have failed to achieve desired glucose control, despite optimal insulin therapy. Appropriate candidates for pramlintide therapy, as illustrated in the previous cases, include those:
- with an A1C < 9%,
- who are actively involved in the management of their diabetes,
- who are experiencing suboptimal glycemic control, especially during the postprandial period, and
- without a history of recurrent, severe hypoglycemia or hypoglycemia unawareness.

Additional information about patient selection can be found in the pramlintide prescribing information.[46]

Pramlintide therapy should be initiated under careful clinical guidance, as directed in the prescribing information. To reduce the risk of hypoglycemia during pramlintide initiation, mealtime insulin should be reduced by 50% in all patients and further adjusted based on SMBG results. In clinical trials where insulin doses were adjusted, the reduction in mealtime insulin by 6 months was ~ 10% for patients with type 2 and 22–28% for patients with type 1 diabetes.[38,39,45] Pramlintide should be initiated gradually and increased as tolerated every three to seven days to reduce the risk of nausea (Table 2). If the patient is experiencing nausea, delay increasing the dose to the next titration level. Once the target dosage of pramlintide is achieved (60 µg for patients with type 1 diabetes and 120 µg for patients with type 2 diabetes, or 10 and 20 units, respectively) and nausea (if any) has subsided, insulin dosages should be further adjusted under the guidance of a health care provider to optimize glycemic control.

Safety and Adverse Events
As with medications generally, use of pramlintide may be associated with adverse events. In clinical trials of pramlintide, the most common treatment-emergent adverse events observed were mild to moderate gastrointestinal events, most notably mild to moderate nausea.[41–44] In addition, insulin-induced severe hypoglycemia occurred more frequently in patients with type 1 diabetes using pramlintide. Nausea and hypoglycemia were more prevalent during the initial clinical trials that used fixed insulin and pramlintide dosing during the initiation period.

Pramlintide alone does not cause hypoglycemia. The hypoglycemia observed in the pramlintide trials was insulin induced, a result of the co-administration of pramlintide with insulin. In early, blinded clinical trials, the event rate for medically assisted severe hypoglycemia during the first 3 months of therapy was greater in pramlintide-treated patients than in those treated with placebo, but the cumulative incidence was less than placebo for the total study period.[46] In a later, open-label study in patients with type 1 diabetes, insulin dosing was reduced during pramlintide initiation, which resulted in an event rate for severe hypoglycemia that was lower than that seen in the earlier studies.

Nausea was more frequent in patients with type 1 diabetes, was primarily mild in nature, occurred more frequently during initiation of pramlintide, and decreased with time.

Key Recommendations
Initiation and use of pramlintide benefit from a focused commitment on the part of both patients and their health care providers. Frequent communication, especially during the initiation and titration of pramlintide therapy, provides guidance and reassurance to patients as they begin a new therapy. Clinical considerations for initiation and use of pramlintide are summarized below:
- Start pramlintide therapy at a low dose and slowly titrate based on type of diabetes and tolerability. If nausea is experienced, consider the following:
  ⇒ Assess the timing of meals relative to pramlintide administration,
  ⇒ Educate patients to recognize

that pramlintide may cause early satiety, or a sense of fullness, and

⇒ Inform patients that they may become uncomfortable or experience nausea if eating continues past the sensation of fullness.

- Reduce premeal insulin to reduce the risk of severe insulin-induced hypoglycemia.
- Increase SMBG to six to eight times a day while initiating pramlintide therapy to determine the patient's postprandial response and reduce the risk of hypoglycemia.
- Adjust insulin doses (both mealtime and basal doses) based on SMBG and overall glycemic response.
- Be aware of the patient's eating habits. Insulin recommendations will differ for patients who eat small quantities all day long ("grazers") compared to those who eat three large meals.

Pramlintide provides another therapeutic option for patients with type 1 or type 2 diabetes who use mealtime insulin and are unable to achieve adequate glycemic control, particularly during the postprandial period. Appropriate patient education is key to successful integration of any new therapy. In addition to understanding what a drug does and how it should be given, patients need to understand what they can reasonably expect from a new therapy. The initial titration of pramlintide and adjustment of insulin require careful attention and vigilance. Patients will benefit from close communication and collaboration with and support from their health care providers.

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