



JOURNAL SCAN

SUMMARY OF KEY ARTICLES

Identifying Challenges With Insulin Therapy and Assessing Treatment Strategies With Pramlintide

INTRODUCTION BY STEVEN V. EDELMAN, MD

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Journal of Diabetes and Its Complications	5	Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? <i>J Diabetes Complications</i> . 2005;19(3):178-181.
Diabetes Care	6	Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA _{1C} . <i>Diabetes Care</i> . 2003;26(3):881-885.
New England Journal of Medicine	7	Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. <i>N Engl J Med</i> . 2007;357(17):1716-1730.
New England Journal of Medicine	8	Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. <i>N Engl J Med</i> . 2008;358(24):2545-2559.
Diabetes Technology & Therapeutics	9	Karl D, Philis-Tsimikas A, Darsow T, et al. Pramlintide as an adjunct to insulin in patients with type 2 diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. <i>Diabetes Technol Ther</i> . 2007;9(2):191-199.
Diabetes Care	10	Hollander PA, Levy P, Fineman MS, et al. 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. <i>Diabetes Care</i> . 2003;26(3):784-790.
Diabetic Medicine	11	Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: A 1-year, randomized controlled trial. <i>Diabet Med</i> . 2004;21(11):1204-1212.

For a full copy of these articles, please refer to the publisher's website or visit www.ncbi.nlm.nih.gov/pubmed.

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INTRODUCTION

Identifying Challenges With Insulin Therapy and Assessing Treatment Strategies With Pramlintide

By Steven V. Edelman, MD

Evidence-based studies continue to provide insights into the difficult clinical challenges with insulin therapy, as well as the clinical value of adjunctive therapies. There are several common issues when treating patients with insulin, which can lead to frustration for healthcare providers and patients. Weight gain, hypoglycemia, glucose fluctuations, and an inability to control postprandial plasma glucose (PPG) values are just a few of the unresolved challenges providers and patients face when trying to achieve glycemic control with insulin therapy. SYMLIN® (pramlintide acetate) injection is an adjunctive therapy—that is, a complement to mealtime insulin—and may fulfill unmet clinical needs in patients with type 2 and type 1 diabetes. SYMLIN, a synthetic peptide of human amylin (another β -cell hormone that is deficient in patients with diabetes), is indicated as an adjunct treatment for patients with type 2 or type 1 diabetes who use mealtime insulin and have not achieved glucose control despite optimal insulin therapy (with or without a concurrent sulfonylurea agent and/or metformin in type 2 diabetes). Clinical studies consistently show significant positive results with the addition of SYMLIN to mealtime insulin therapy in terms of helping patients achieve glucose homeostasis (improved A1C, lower postprandial glucose levels, and reduced glucose fluctuations) and reduce their insulin requirements while simultaneously experiencing weight loss.*†

THE BURGEONING ROLE OF PPG

The gold standard for glycemic control for years has been glycosylated hemoglobin (A1C), which represents only the average blood glucose levels over the past 2 to 3 months. Hirsch and Brownlee postulate that glucose variability, in combination with A1C, may be a more reliable indicator of glycemic control and the risk for complications than is A1C alone.¹ The glucose values of patients without diabetes will typically vary within a very narrow range compared with what is observed in insulin-treated patients. The body of data in the literature suggests that there are deleterious effects associated with glucose variability; however, longer-term outcome studies need to be completed.

Meanwhile, others are further examining current standards by elucidating the relationship between PPG and A1C. Analysis by Monnier et al concludes that PPG directly impacts A1C. In patients with type 2 diabetes, the contribution of PPG to A1C, relative to the contribution of fasting glucose, increases progressively as A1C decreases toward target levels.² Monnier's data help to explain that while treatments that target PPG do lower A1C without causing hypoglycemia, they do not lower A1C as much as treatments that do cause hypoglycemia.²

Trying to mimic what happens in the normal, nondiabetic state makes physiologic sense. A person with diabetes typically has PPG levels that not only are high (around 200 mg/dL)³ but also take several hours to return to baseline.⁴ This is quite abnormal compared with healthy individuals, who rarely have a PPG level above 140 mg/dL,⁴ even after a high-calorie or carbohydrate-dense meal. Research suggests that normalizing PPG, in addition to normalizing fasting plasma glucose, will help achieve long-term glycemic control.²

ASSESSING THE RISKS AND BENEFITS OF INSULIN THERAPY

Many patients do not achieve glycemic control with oral antidiabetic agents, and so they must also use insulin. While insulin may help some patients reach target A1C, the risks associated with increasing doses of insulin, such as weight gain and hypoglycemia, may not always outweigh the benefits. For example, the results of the Treating to Target in Type 2 Diabetes (4-T) study showed that adding and increasing the doses of biphasic, prandial, or basal insulin to maximally tolerated doses of metformin and sulfonylurea helped some patients achieve an A1C of 6.5%, but it led to an increase in hypoglycemic events and weight gain.⁵ The Action to Control Cardiovascular Risk in

*In a 6-month, open-label clinical trial, insulin-using patients with type 2 (n=166) or type 1 (n=265) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Introduction (continued)

Diabetes (ACCORD) study showed that treating patients with intensive therapy to achieve a target A1C of <6.0% increased the incidence of all-cause death, hypoglycemia, and weight gain in patients with type 2 diabetes and risk factors for cardiovascular disease (CVD) or previous cardiovascular events.⁶

NEW TREATMENT STRATEGIES WITH PRAMLINTIDE

In an effort to address the unresolved challenges of insulin therapy, investigators have reported on SYMLIN® (pramlintide acetate) injection as an amylin replacement and an adjunct to insulin in patients with type 2 and type 1 diabetes. Karl et al, for example, note that adding pramlintide to mealtime insulin resulted in a reduction in PPG and A1C in patients with type 2 diabetes, as well as a reduction in weight and in insulin requirements.⁷

In a 1-year controlled trial, Hollander et al found that the addition of SYMLIN to the existing mealtime insulin therapy of patients with type 2 diabetes led to an improvement in long-term glycemic control and to a greater proportion of patients achieving glycemic targets, compared with patients using insulin therapy alone. Additionally, this glycemic improvement occurred without weight gain and without an increase in the rate of severe hypoglycemia.⁸ Similar results were reported in a controlled study of 651 patients with type 1 diabetes who were taking mealtime insulin. Ratner et al found that mealtime replacement of amylin with SYMLIN as an adjunct to insulin therapy improved long-term glycemic and weight control.⁹

These seven studies, summarized in this *Journal Scan*, point to the challenges of managing hyperglycemia in patients who require insulin therapy—weight gain, hypoglycemia, glycemic variability, and an inability to reach glycemic targets—and indicate that clinicians should consider new treatment strategies to address these unmet needs. The addition of SYMLIN to mealtime insulin may help overcome many unresolved challenges of insulin therapy. The research findings in this *Journal Scan* supplement provide cli-

nicians with information that can bring about positive results in the clinical care of patients with type 2 diabetes who use insulin and patients with type 1 diabetes. ■

Please see the Important Safety Information on page 12 and the accompanying SYMLIN Prescribing Information, including the **Boxed Warning regarding insulin-induced severe hypoglycemia**.

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WARNING

SYMLIN is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

Should Minimal Blood Glucose Variability Become the Gold Standard of Glycemic Control?

Key Point: Along with a reduction in A1C, a reduction in glucose excursions should be a goal of treatment, as they have been shown to accelerate the development of long-term complications of diabetes.

Glycosylated hemoglobin (A1C) has been—and continues to be—the gold standard of glycemic control, with levels $\leq 7\%$ being the benchmark for reducing the risk for vascular complications. Diabetes Complications and Control Trial (DCCT) investigators questioned these standards by investigating whether aspects of glucose homeostasis, auxiliary to A1C, could affect the development or progression of microvascular complications. In a 1995 report, DCCT investigators concluded that even when A1C levels were comparable for both intensively treated patients and their conventionally treated counterparts, the latter group experienced a markedly higher risk for progression of retinopathy over time.

INVESTIGATORS' HYPOTHESIS OF PHENOMENON

This higher risk for retinopathy may be due to the increased frequency and magnitude of glycemic excursions in conventionally treated patients, who received fewer insulin injections than did patients in the intensive group. The investigators also postulated that the intensity of this glycemic variability would stimulate the reactive oxygen species (ROS) in complications-prone cells. The overproduction of ROS by the mitochondrial electron-transport

chain during periods of hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-mediated vascular damage.

Quantifying oxidative stress in relation to glycemia has provided added insight into the ways in which acute hyperglycemia affects aspects of physiologic homeostasis. Based on this emerging evidence, Hirsch and Brownlee hypothesize that glucose excursions and mean A1C are more reliable indicators of blood glucose control and risk for long-term complications than is mean A1C alone.

ASSESSING THE QUALITY OF GLYCEMIC CONTROL

The investigators suggest that the results of the cited studies support their hypothesis that both postprandial and daily glucose excursions may be important but underappreciated mechanisms resulting in ROS accumulation, which in turn accelerates micro- and macrovascular disease. Furthermore, the risk for diabetic complications may be misestimated when the prognostic significance of large glycemic variability is overlooked because mean A1C levels are within or near normal range. Thus, there may be benefit in shifting the focus of therapy toward the stabilization of glucose variability in patients with diabetes, even if A1C remains the same. ■

Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients

Key Point: In addition to A1C, PPG is an important measure of glycemic control. It has been shown that the contribution of PPG to A1C, relative to fasting glucose, increases as A1C decreases toward goal.

Although previous studies suggest that postprandial hyperglycemia contributes to approximately 30% to 40% of the total daytime hyperglycemia, its exact contribution to the overall glycemic control of patients with type 2 diabetes remains largely unknown. The discrepancies in the data published previously might be explained by the interference of several factors. To test the specific effect of PPG levels on overall glycemic control, Monnier, Lapinski, and Colette analyzed the diurnal glycemic profiles of patients with type 2 diabetes with different levels of A1C.

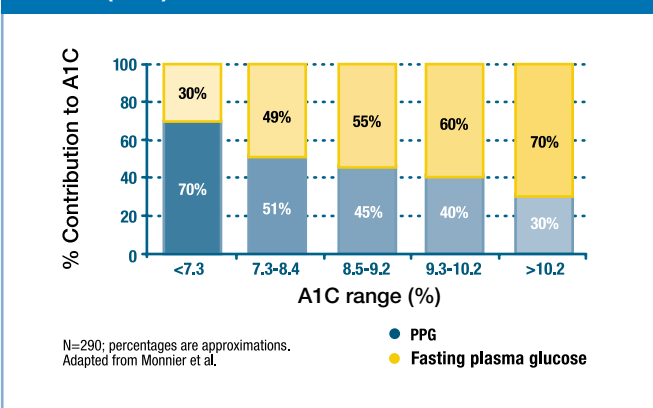
RESEARCH DESIGN AND METHODS

In 290 non-insulin- and non-carbose-using patients with type 2 diabetes, plasma glucose concentrations were determined at fasting (8:00 AM) and during postprandial and postabsorptive periods (at 11:00 AM, 2:00 PM, and 5:00 PM). The areas under the curve above fasting glucose concentrations (AUC_1) and >109.91 mg/dL (>6.1 mmol/L) (AUC_2) were calculated for further evaluation of the relative contributions of postprandial (AUC_1/AUC_2 , %) and fasting ($[AUC_2 - AUC_1]/AUC_2$, %) plasma glucose increments to the overall diurnal hyperglycemia. The data were compared over quintiles of A1C.

RESULTS

As shown in the Figure, the relative contribution of PPG decreased progressively from the lowest (69.7%) to the highest quintile of A1C (30.5%, $P < 0.001$). By contrast, the relative contribution of fasting glucose increased gradually with increasing levels of A1C: 30.3% in the lowest to 69.5% in the highest quintile ($P < 0.001$).

Figure. Increase in Contribution of Postprandial Plasma Glucose (PPG) as A1C Decreases



CONCLUSIONS

According to the investigators, the study results suggest that postprandial glycemic excursions play a major role in the metabolic disequilibrium that is characteristic of patients with mild to moderate hyperglycemia. While fasting hyperglycemia has a large impact on the overall diurnal hyperglycemia experienced by patients with poorly controlled diabetes, PPG elevations play a larger role in glycemic control as patients advance from poorly controlled to controlled diabetes. The importance of postprandial glycemic excursions in patients with fairly well-controlled type 2 diabetes is in agreement with the results of all epidemiological studies. These results are of particular importance when we consider that compared with fasting hyperglycemia, postprandial hyperglycemia has been shown to be a stronger predictor of vascular disease. ■

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Key Point: Despite adding increasing doses of mealtime insulin, a minority of patients overall achieved targeted A1C levels, while the majority of patients gained weight and had an increase in hypoglycemic events. Pramlintide was not included in this study.

Type 2 diabetes mellitus is a progressive condition characterized by the continual increase in glucose levels and the dysfunction of beta cells. While the maintenance of nearly normal glycemic levels reduces the risk for diabetic complications, it is difficult to achieve, despite the use of mounting doses of oral antidiabetic agents and the addition of insulin to that regimen. Many patients do not reach targets for glycated hemoglobin (A1C) with this regimen, and there is often great concern regarding the increased risk for hypoglycemia and weight gain. Treating to Target in Type 2 Diabetes (4-T) is a 3-year, multicenter, open-label, randomized, controlled clinical trial that compared the efficacy and safety of adding analogue biphasic, prandial, or basal insulin to the treatment of patients with type 2 diabetes who had suboptimal glycemic control while receiving maximally tolerated doses of metformin and sulfonylurea.

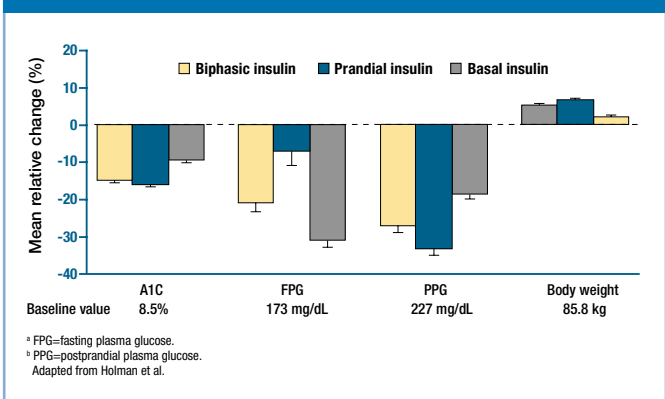
METHODS

The investigators enrolled 708 adults with a suboptimal A1C (7.0% to 10.0%) who were receiving maximally tolerated doses of metformin and sulfonylurea. Patients were randomized to receive twice-daily biphasic insulin aspart, thrice-daily prandial insulin aspart, or once-daily basal insulin detemir (twice if required). The primary outcome measure at 1 year was the mean A1C. Secondary outcome measures included the proportion of patients with an A1C of 6.5% or less, the rate of hypoglycemia, and weight gain.

RESULTS

The maximal reduction in the mean A1C occurred by 24 weeks with the use of escalating doses of insulin and then remained stable. At 52 weeks, the reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group. The respective proportions of patients with an A1C of 6.5% or less were 17.0%, 23.9%, and 8.1%; respective proportions of patients with an A1C of 6.5% or less and without hypo-

Figure. Mean (\pm SE) Percentage Change From Baseline to 1 Year in A1C, FPG,^a PPG,^b and Body Weight



glycemia (grade 2 or more) between weeks 48 and 52 were 52.5%, 43.9%, and 78.9% ($P=0.001$). Insulin usage continually increased across all groups, and by week 52, patients in the prandial group were using the highest dose. Weight also increased across all groups, with patients in the prandial group experiencing the greatest increase (5.7 kg, 4.7 kg in the biphasic group, and 1.9 kg in the basal group). Mean numbers of hypoglycemic events (grade 2 or more) per patient per year in the biphasic, prandial, and basal groups were 5.7, 12.0, and 2.3, respectively.

CONCLUSIONS

Holman and colleagues concluded that a single analogue-insulin formulation added to metformin and sulfonylurea resulted in an A1C of 6.5% or less in a minority of patients at 1 year. Maximal glycemic control appears to happen around week 24. Further reductions were not achieved, despite escalating doses of insulin. Glucose lowering was achieved at the expense of weight gain and an increased risk for hypoglycemia, particularly with the biphasic and prandial regimens. Prandial insulin lowered A1C to the same extent as did biphasic insulin, but with twice the episodes of hypoglycemia and an increase in weight gain of 21%. ■

Effects of Intensive Glucose Lowering in Type 2 Diabetes

Key Point: Patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study who received intensive treatment had more hypoglycemia and weight gain than those who received standard treatment. An increase in all-cause mortality among patients in the intensive treatment group was also found. This study suggests that the risks associated with intensive therapy used to lower A1C below standard recommended levels may outweigh the benefits of such treatment. Pramlintide was not included in this study.

The ACCORD trial assessed whether intensive treatment that targets A1C below 6.0% would reduce cardiovascular events more than do treatments that aim to reduce A1C to between 7.0% and 7.9% in patients with type 2 diabetes and either with risk factors for or with established cardiovascular disease (CVD).

METHODS

Patients with type 2 diabetes (mean age, 62.2 years, median A1C of 8.1%) and a history of CVD or risk factors for CVD (35% had a previous cardiovascular event) were randomized to the intensive and standard therapy treatment groups. The primary outcome was the occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or death from cardiovascular causes. After 3.5 years, the study was discontinued because of the increase in rate of death in the intensive treatment group.

RESULTS

After 4 months with treatment, median A1C had fallen from the baseline median of 8.1% to 6.7% in the intensive treatment group and to 7.5% in the standard treatment group. Median A1Cs of 6.4% and 7.5% were achieved by the intensive and standard treatment groups, respectively, at 1 year and were maintained during follow-up. Patients in the intensive group were exposed to a greater number of

treatments and had more frequent changes in the dose or number of treatments.

Compared with the standard treatment group, the intensive treatment group had a significantly higher incidence of hypoglycemia requiring medical assistance (10.5% vs 3.5%, $P < 0.001$) and weight gain > 10 kg from baseline (27.8% vs 14.1%, $P < 0.001$). Also, the rate of nonfatal MI was lower in the intensive group than in the standard group (3.6% vs 4.6%, $P = 0.004$), but the rate of death from any cause was higher (5.0% vs 4.0%, $P = 0.04$). The rate of death began to separate after 1 year and continued throughout follow-up.

CONCLUSIONS

This study showed that using intensive therapy to target an A1C below 6.0% in patients with type 2 diabetes and risk factors for CVD or previous CVD events resulted in an increase in mortality compared with patients who received standard therapy and who had a targeted A1C between 7.0% and 7.9%. This increase equates to one extra death for every 95 patients who were treated over 3.5 years. The results suggest that the potential benefit (reduction in number of nonfatal MIs) of intensive glucose lowering may not be seen for several years, during which time there is a marked increase in the risk for death from any cause. ■

Pramlintide as an Adjunct to Insulin in Patients With Type 2 Diabetes in a Clinical Practice Setting Reduced A1C, Postprandial Glucose Excursions, and Weight

Key Point: When taken with mealtime insulin, pramlintide, an analogue of the hormone amylin, reduced A1C and controlled postprandial plasma glucose (PPG) excursions by slowing gastric emptying and regulating food intake, which resulted in weight loss.*,†

The neuroendocrine hormone amylin—deficient in patients with diabetes due to pancreatic β-cell dysfunction—works in concert with insulin to modulate PPG levels by slowing gastric emptying, suppressing postprandial glucagon secretion, and regulating food intake. Pramlintide is an amylin analogue that, when taken with mealtime insulin in patients with type 2 or type 1 diabetes, has been shown to reduce PPG excursions, A1C, and weight when compared with insulin alone. Karl et al examined the efficacy and safety of pramlintide in patients with type 2 and type 1 diabetes in the clinical practice setting and report the results in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this uncontrolled, open-label study, 166 patients with type 2 diabetes and a mean A1C of 8.3% added 120 μg of pramlintide to their existing mealtime insulin therapy. At treatment initiation, mealtime insulin doses were reduced 30% to 50% to reduce the risk for hypoglycemia. After pramlintide tolerability was established, doses of basal and mealtime insulin were adjusted, based on the results of self-monitored blood glucose levels, to achieve optimal glucose control. Endpoints included safety, change in A1C, PPG, weight, and insulin doses, as well as responses to a treatment-satisfaction survey given at 6 months.

RESULTS

At 6 months, patients had a significant reduction in A1C (−0.56%, $P < 0.05$) and weight (−2.8 ± 0.34 kg, $P < 0.05$). A significant reduction in mealtime and basal insulin doses was made during the first 4 weeks of treatment (−21.6% and −12.9%, respectively, $P < 0.05$), with results showing a total mean reduction in insulin use of −6.4% ± 2.66%. After 6 months of treatment, patients reported better overall glucose management, with 80% of patients reporting that taking the extra injections each day was easy or very easy.

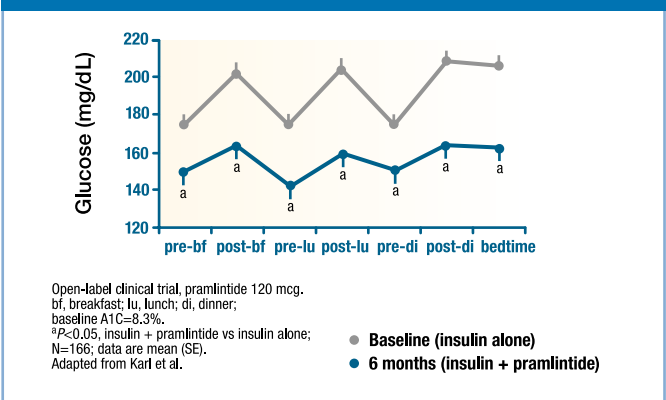
* In a 6-month, open-label clinical trial, insulin-using patients with type 2 (n=166) or type 1 (n=265) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

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Based on Karl D, Philis-Tsimikas A, Darsow T, et al. Pramlintide as an adjunct to insulin in patients with type 2 diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. *Diabetes Technol Ther.* 2007;9(2):191-199.

Figure. Type 2 Diabetes: Change in Glucose Profile



Ninety-eight percent of patients reported they would like to continue pramlintide treatment.

Results of seven-point glucose profiles showed that patients taking pramlintide experienced fewer and less severe PPG fluctuations at 6 months than at baseline ($P < 0.05$) (Figure).

Karl et al found pramlintide to be generally well tolerated. Overall, 12% of patients experienced hypoglycemia during the 6-month treatment period, with only two patients reporting severe hypoglycemia (0.04 ± 0.02 events per patient-year). Mild-to-moderate nausea was reported by 29.5% of patients receiving a 120-μg dose and was found to be most common during treatment initiation.

CONCLUSION

Despite the use of insulin and oral medications, many patients with diabetes are unable to achieve the desired glucose targets. This study shows that the addition of pramlintide facilitates a reduction in A1C, PPG, and weight while also reducing insulin doses. The reduction in PPG is of particular interest in light of the findings of recent studies suggesting that PPG plays a greater role than fasting glucose in overall glycemic control. ■

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

Key Point: The addition of pramlintide to insulin therapy has been shown to reduce A1C and weight without increasing the incidence of hypoglycemia.*,†

Despite important advances in insulin therapy, most patients with type 2 diabetes are unable to achieve satisfactory glycemic control. Satisfactory glycemic control with insulin is often intercepted by excessive weight gain, failure to adequately control postprandial glycemic (PPG) excursions, and an increased risk for hypoglycemia. However, the advent of adjunct mealtime amylin replacement with the human amylin analogue pramlintide has been shown to reduce PPG excursions in patients with type 2 diabetes. This study assessed the long-term efficacy and safety of pramlintide in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

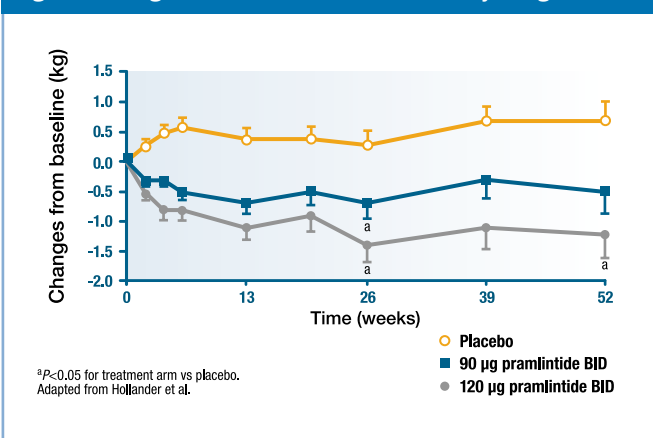
In a 52-week, double-blind, placebo-controlled, parallel-group, multicenter study, 656 patients with type 2 diabetes (age 57 ± 10 years, diabetes duration 12 ± 7 years, body mass index 34.0 ± 7.0 kg/m², A1C $9.1\% \pm 1.2\%$, mean \pm standard deviation) treated with insulin (alone or in combination with sulfonylureas and/or metformin) were randomized to receive additional subcutaneous injections of either placebo or pramlintide (60 μ g 3 times a day [TID], 90 μ g twice a day [BID], or 120 μ g BID).

RESULTS

Hollander et al showed that treatment with pramlintide 120 μ g BID led to a sustained reduction from baseline in A1C (-0.68% and -0.62% at 26 and 52 weeks, respectively). This was significantly greater than that in the placebo group ($P < 0.05$). In the patients receiving pramlintide in addition to their insulin, an almost twofold greater proportion achieved an A1C $< 8\%$ (90 μ g BID group 42.4% and 120 μ g BID 45.7%) compared with the patients receiving placebo plus insulin (27.6%).

Patients in the pramlintide group achieved a greater reduction in weight without increasing body weight. In fact, patients in both pramlintide treatment groups had a significant reduction in body weight by week 26 (both $P < 0.05$)

Figure. Change From Baseline in Mean Body Weight



(Figure). Patients in the 120 μ g BID treatment group sustained this reduction to week 52 ($P < 0.05$ vs placebo).

The greater reductions in A1C in the pramlintide treatment groups were not associated with an overall increase in severe hypoglycemia. Nausea and headache were the only treatment-emergent adverse events that occurred in $\geq 10\%$ of patients in the pramlintide treatment groups. Nausea was usually mild to moderate and transient. The majority of pramlintide-treated patients did not experience nausea during the study, and only 2% to 4% experienced severe nausea.

CONCLUSIONS

Hollander et al concluded that adding pramlintide to the existing mealtime insulin regimen of patients with type 2 diabetes leads to improved long-term glycemic control. Furthermore, an increased proportion of patients achieved glycemic targets beyond those obtained with insulin therapy alone. Notably, this improvement in A1C was attained without weight gain and without an increase in the overall incidence of severe hypoglycemia. Pramlintide was generally well tolerated, with nausea being mild to moderate and transient. ■

* In a 6-month, open-label clinical trial, insulin-using patients with type 2 ($n = 166$) or type 1 ($n = 265$) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Please see the Important Safety Information on page 12 and the accompanying SYMLIN Prescribing Information, including the Boxed Warning regarding insulin-induced severe hypoglycemia.

Based on Hollander PA, Levy P, Fineman MS, et al. 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. *Diabetes Care*. 2003;26(3):784-790.

Amylin Replacement With Pramlintide as an Adjunct to Insulin Therapy Improves Long-Term Glycaemic and Weight Control in Type 1 Diabetes Mellitus: A 1-Year, Randomized Controlled Trial

Key Point: Adding pramlintide to insulin therapy reduced A1C and weight without increasing insulin use or the risk for hypoglycemia, and with only mild-to-moderate nausea.*,†

In patients with type 1 diabetes, abnormal autoimmune responses cause the destruction of pancreatic β cells, resulting in the deficiency of two glucoregulatory peptide hormones, insulin and amylin. Most patients have a very difficult time achieving glycaemic goals with insulin replacement alone. In this study, Ratner et al aimed to determine the long-term efficacy and safety of adjunctive therapy with pramlintide, a synthetic human amylin analogue, in patients with type 1 diabetes. By replacing amylin, pramlintide may offer patients with type 1 diabetes improved glycaemic control without weight gain.

RESEARCH DESIGN AND METHODS

In a double-blind, placebo-controlled, parallel-group, multicenter study, 651 patients with type 1 diabetes (age 41 ± 13 years, A1C $8.9\% \pm 1.0\%$, mean \pm standard deviation) were randomized to receive mealtime injections of placebo or varying doses of pramlintide, in addition to their insulin therapy, for 52 weeks.

RESULTS

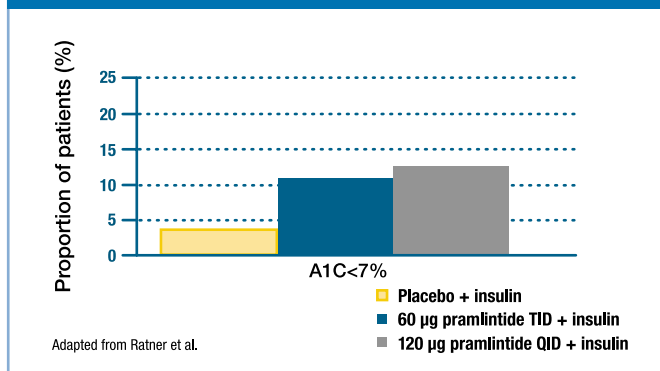
The addition of both 60 μ g 3 times a day (TID) and 60 μ g 4 times a day (QID) pramlintide to insulin therapy led to significant reductions in A1C from baseline to week 52 (0.29%, $P=0.011$ and 0.34%, $P=0.001$, respectively), compared with the placebo group (0.04%) (Figure). Furthermore, three times the proportion of patients in both pramlintide treatment groups achieved an A1C $<7\%$, compared with the placebo group.

Patients in the pramlintide group were able to achieve these A1C reductions without an increase in insulin doses. Patients in the 60 μ g TID group decreased insulin use by 3% and patients in the 60 μ g QID group decreased insulin use by 6%, compared with patients in the placebo group, who had no change.

* In a 6-month, open-label clinical trial, insulin-using patients with type 2 ($n=166$) or type 1 ($n=265$) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Figure. Proportion of Patients Achieving an A1C $<7\%$ at Any Time During the Study



The improvement in A1C with pramlintide was associated with a significant reduction in body weight from baseline to week 52 of 0.4 kg in the 60 μ g TID ($P<0.027$) and QID ($P<0.040$) pramlintide treatment groups, compared with a 0.8-kg gain in body weight in the placebo group. When data on mean change in weight were stratified by baseline body mass index, results showed not only that pramlintide prevented weight gain in lean patients but also that it induced weight loss in overweight and obese patients.

Mild-to-moderate nausea was the most common adverse event in pramlintide-treated patients. Most nausea was transient and occurred early (within the first 4 weeks) in treatment.

CONCLUSIONS

Ratner et al concluded that for patients with type 1 diabetes taking insulin, replacement of amylin with 60 μ g of mealtime pramlintide improves weight and long-term glycaemic control via reductions in postprandial glucose. These improvements were achieved without increases in insulin use. ■

Important Safety Information for SYMLIN® (pramlintide acetate) Injection

WARNING

SYMLIN is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

INDICATIONS AND USAGE

SYMLIN is given at mealtimes and is indicated for:

- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.
- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

CONTRAINDICATIONS

Hypersensitivity to SYMLIN or any of its components, including metacresol; confirmed diagnosis of gastroparesis; hypoglycemia unawareness.

WARNINGS

Patient Selection. Proper patient selection is critical to safe and effective use of SYMLIN. SYMLIN therapy should only be considered in patients with insulin-using type 2 or type 1 diabetes who fulfill the following criteria:

- have failed to achieve adequate glycemic control despite individualized insulin management;
- are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for SYMLIN therapy:

- poor compliance with current insulin regimen;
- poor compliance with prescribed self-blood glucose monitoring;
- have an HbA1c >9%;
- recurrent severe hypoglycemia requiring assistance during the past 6 months;
- presence of hypoglycemia unawareness;
- confirmed diagnosis of gastroparesis;
- require the use of drugs that stimulate gastrointestinal motility;
- pediatric patients.

Hypoglycemia. SYMLIN alone does not cause hypoglycemia. However, SYMLIN is indicated to be co-administered with insulin therapy and in this setting SYMLIN increases the risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Therefore, when introducing SYMLIN therapy, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin.

ADVERSE EVENTS

The most common adverse event was nausea, which decreased with time in most patients. For adverse events regarding severe hypoglycemia, see WARNINGS.

Please see the accompanying SYMLIN Prescribing Information.

Symlin[®]

(pramlintide acetate)
injection

Medication Guide

SYMLIN[®] (SĪM-lĭn) (pramlintide acetate) injection

Read the Medication Guide and the "Patient Instructions for Use" that come with your SYMLIN product before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about SYMLIN?

- SYMLIN is used with insulin to lower blood sugar, especially high blood sugar that happens after meals.
- SYMLIN is given at mealtimes. The use of SYMLIN does not replace your daily insulin but may lower the amount of insulin you need, especially before meals.
- Even when SYMLIN is carefully added to your mealtime insulin therapy, your blood sugar may drop too low, especially if you have type 1 diabetes. If this low blood sugar (severe hypoglycemia) happens, it is seen within 3 hours after a SYMLIN injection. Severe low blood sugar makes it hard to think clearly, drive a car, use heavy machinery or do other risky activities where you could hurt yourself or others.
- SYMLIN should only be used by people with type 2 and type 1 diabetes who:
 - already use their insulin as prescribed, but still need better blood sugar control.
 - will follow their doctor's instructions exactly.
 - will follow up with their doctor often.
 - will test their blood sugar levels before and after every meal, and at bedtime.
 - understand how to adjust SYMLIN and insulin doses.

What is SYMLIN?

SYMLIN is an injectable medicine for adults with type 2 and type 1 diabetes to control blood sugar. SYMLIN slows down the movement of food through your stomach. This affects how fast sugar enters your blood after eating. SYMLIN is always used with insulin to help lower blood sugar during the 3 hours after meals.

Who should not use SYMLIN?

Do not use SYMLIN if you:

- cannot tell when your blood sugar is low (hypoglycemia unawareness).
- have a stomach problem called gastroparesis. This is when your stomach does not empty as fast as it should.
- are allergic to SYMLIN or any ingredients in SYMLIN. See the end of this Medication Guide for a complete list of ingredients.

SYMLIN has not been studied in children.

What should I tell my doctor before starting SYMLIN?

Tell your doctor about all of your medical conditions including if you:

- are pregnant or planning to become pregnant. It is not known if SYMLIN can harm your unborn baby. You and your doctor will decide how to best control your blood sugar levels during pregnancy.
- are breastfeeding. It is not known if SYMLIN passes into your milk and if it can harm your baby. You and your doctor will decide the best way to feed your baby if you are using SYMLIN.

Keep a list of all the medicines you take. Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and

herbal supplements. SYMLIN can slow down how other medicines pass through your stomach and may affect how much of them get into your body. You may have to change the times you take certain medicines.

How should I use SYMLIN?

- You must use SYMLIN exactly as prescribed. The amount of SYMLIN you use will depend on whether you have type 2 or type 1 diabetes. You and your doctor will decide if you can use SYMLIN.
- It is important for you to carefully read, understand and follow the "Patient Instructions for Use" that comes along with this Medication Guide and your SYMLIN.
- SYMLIN is available in vials and two SymlinPen[®] pen-injectors. Your doctor will prescribe the type of SYMLIN that is right for you.
 - If you have been using the SYMLIN vial with an insulin syringe and you are changing to the SymlinPen[®] pen-injector: **Your doctor will prescribe the SymlinPen[®] pen-injector that is right for you, tell you how much SYMLIN to inject and when to inject it.**
 - **It is important that you understand how to inject the right SYMLIN dose. Read the "Patient Instructions for Use" carefully BEFORE giving your first dose with the SymlinPen[®] pen-injector. The SYMLIN in the pen-injector is a different strength than the SYMLIN in the vial.**
- The way you inject SYMLIN is similar to the way you inject insulin. **Inject SYMLIN under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh).** Inject SYMLIN at a site that is more than 2 inches away from your insulin injection. Do not inject SYMLIN and insulin in the same site.
- To help reduce the chances of getting a reaction at the injection site, allow SYMLIN to come to room temperature before injecting.
- Use a new needle for each SYMLIN injection.
- **Never mix SYMLIN and insulin.** Insulin can affect SYMLIN when the two are mixed together.
- Do not use SYMLIN if the liquid looks cloudy.
- If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and you may not be able to eat the amount of food you usually eat. If you take more SYMLIN than your prescribed dose, pay careful attention to the amount of insulin you use because you may be at more risk for low blood sugar. Contact your doctor for guidance.
- If you miss or forget a dose of SYMLIN, wait until the next meal and take your usual dose of SYMLIN at that meal. **Do not take more than your usual dose of SYMLIN.**

Using SYMLIN and insulin with Type 2 Diabetes

1. Start SYMLIN at 60 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. Reduce your rapid-acting or short-acting insulin, including fixed-mix insulin such as 70/30, used before meals by **50 percent**. This means half of the dose you usually use.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 120 mcg on your doctor's instructions if you have not had any nausea for 3 days or more.
5. Tell your doctor right away if you have nausea with the 120 mcg dose. Your doctor will tell you how to adjust your dose of SYMLIN.
6. Your doctor may make changes to your insulin doses to better control your blood sugar once you are using the 120 mcg dose of SYMLIN. All insulin changes should be directed by your doctor.

Using SYMLIN and insulin with Type 1 Diabetes

1. Start SYMLIN at 15 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. When starting SYMLIN, reduce your rapid-acting or short-acting insulin, including fixed-mix insulin such as 70/30, used before meals by **50 percent**. This means half of the dose you usually use. All insulin changes should be directed by your doctor.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 30 mcg on your doctor's instructions if you have not had any nausea for 3 days or more. If you have nausea with SYMLIN at 30 mcg, call your doctor right away. Your doctor may decide that you should stop SYMLIN.
5. Increase your dose of SYMLIN to 45 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 30 mcg dose.

- Increase your dose of SYMLIN to 60 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 45 mcg dose.
- Call your doctor right away if you are bothered with nausea on the 45 mcg or 60 mcg dose. Your doctor may decide that you should reduce SYMLIN to the 30 mcg dose.
- Your doctor may make changes to your insulin doses to better control your blood sugar once you are on a dose of SYMLIN that is right for you. All insulin changes should be directed by your doctor.

Staying on SYMLIN

- Once you reach your recommended dose of SYMLIN, talk to your doctor about changing your insulin doses to better control your blood sugar. You may have to increase your long-acting insulin to prevent high blood sugar (hyperglycemia) between meals. **Insulin changes should always be directed by your doctor based on blood sugar testing.**
- Call your doctor if nausea or low blood sugar continues while on your recommended dose of SYMLIN. Low blood sugar that happens often is a warning sign of possible severe low blood sugar, especially if you have type 1 diabetes.
- If you stop taking SYMLIN for any reason, such as surgery or illness, talk to your doctor about how to re-start SYMLIN.**

When should I not use SYMLIN?

Do not use SYMLIN if:

- your blood sugar is too low.
- you do not plan to eat. Do not inject SYMLIN if you skip a meal.
- you plan to eat a meal with less than 250 calories or 30 grams of carbohydrate.
- you are sick and can't eat your usual meal.
- you are having surgery or a medical test where you cannot eat.
- you are pregnant or breastfeeding and have not talked to your doctor.

Talk to your doctor if you have any of these conditions.

What should I avoid while taking SYMLIN?

- Do not drive or operate dangerous machinery until you know how SYMLIN affects your blood sugar. Low blood sugar makes it hard to think clearly, drive a car, use heavy machinery or do other risky activities where you could hurt yourself or others. Discuss with your doctor what activities you should avoid.
- Alcohol may increase the risk of low blood sugar.
- Your doctor will tell you which medicines you can take while using SYMLIN. Do not take other medicines that slow stomach emptying.**

What are the possible side effects of SYMLIN?

Low blood sugar (hypoglycemia)

- SYMLIN is used with insulin to lower your blood sugar, but your blood sugar may drop too low, especially if you have type 1 diabetes.** See "What is the most important information I should know about SYMLIN?"
- When starting SYMLIN, reduce your doses of insulin before meals as recommended by your doctor to reduce the chance of low blood sugar. You and your doctor should talk about a plan to treat low blood sugar. You should have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon with you at all times. Call your doctor if you have low blood sugar more often than normal or severe low blood sugar.

Your chance for low blood sugar is higher if you:

- do not reduce your insulin dose before meals at the beginning of SYMLIN treatment, as directed by your doctor.
- use more SYMLIN or insulin than prescribed by your doctor.
- change your insulin dose without checking your blood sugar.
- eat less food than your usual meal.
- are sick and cannot eat.
- are more active than usual.
- have a low blood sugar level before eating.
- drink alcohol.

Always have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon available to treat low blood sugar.

Nausea: Nausea is the most common side effect with SYMLIN. Mild nausea is more likely during the first weeks after starting SYMLIN and usually does not last long. It is very important

to start SYMLIN at a low dose and increase it as directed by your doctor. See "How should I use SYMLIN?" If nausea continues or bothers you, call your doctor right away.

Other Side Effects: SYMLIN also may cause the following side effects: decreased appetite, vomiting, stomach pain, tiredness, dizziness, or indigestion.

SYMLIN also can cause reactions at the injection site including redness, minor bruising, or pain. See the detailed "Patient Instructions for Use." Follow the directions under "How should I use SYMLIN?" to reduce the chance of an injection site reaction.

Tell your doctor if you have any side effects that bother you or that do not go away.

These are not all the side effects with SYMLIN. Ask your doctor or pharmacist for more information.

How should I store SYMLIN?

- Store SYMLIN that has not been opened in the refrigerator, between 36° F to 46° F (2° C to 8° C), until you are ready to use it. Protect SYMLIN from light.
- After a vial or pen-injector has been used for the first time, it can be refrigerated or kept at a temperature up to 86° F (30° C) for 30 days. Do not leave **above** 86° F (30° C). Any vial or pen-injector in use should be thrown away after 30 days, even if it still has medicine in it.
- Unused SYMLIN (opened or unopened) should not be used after the expiration (EXP) date printed on the carton and the label.
- Do not freeze SYMLIN. Do not use SYMLIN if it has been frozen.**

Keep SYMLIN and all medicines out of the reach of children.

General information about the safe and effective use of SYMLIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYMLIN for a condition for which it was not prescribed. Do not give SYMLIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SYMLIN. Also see the "Patient Instructions for Use" on using the SymlinPen® pen-injector or vial. You can ask your doctor for more about SYMLIN, including information that is written for doctors.

More information on SYMLIN can be found at <http://www.SYMLIN.com>.

SYMLIN Customer Service is available 24 hours a day at 1-800-349-8919.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What are the ingredients in SYMLIN?

Active ingredient: pramlintide acetate

Inactive ingredients: metacresol, D-mannitol, acetic acid, and sodium acetate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Literature Revised July 2008

Manufactured for Amylin Pharmaceuticals, Inc.

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1-800-349-8919

<http://www.SYMLIN.com>

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