Amylin Replacement With Pramlintide in Type 1 and Type 2 Diabetes: A Physiological Approach to Overcome Barriers With Insulin Therapy

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Long-term intervention studies such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have clearly demonstrated that intensification of diabetes therapy reduces the risk of microvascular and possibly macrovascular complications in both type 1 and type 2 diabetes.[1–4] However, these studies also demonstrated how difficult it is for patients to achieve and sustain tight glycemic control over prolonged periods of time, even with insulin, the most powerful agent in our therapeutic armamentarium.[2–5] Moreover, both studies showed that intensification of therapy, especially with insulin, was accompanied by key clinical shortcomings, namely recurrent severe hypoglycemia and excessive weight gain.[3,6–10] For many patients, these adverse effects of intensive insulin therapy represent the very obstacles that hinder the pursuit of optimal glycemic control.

More recently, important advances in insulin therapy, including the refinement of insulin pump regimens for continuous subcutaneous insulin infusion (CSII) and the development of rapid- and long-acting insulin analogs,[11,12] have offered new hope to both physicians and patients. However, despite the lessons of the DCCT and UKPDS and the improvements of insulin therapy, recent cross-sectional data indicate that, in the general population with diabetes, levels of glycemic control are still far above the glycemic targets set forth by professional diabetes organizations (e.g., the hemoglobin A_{1c} [A1C] target of <7% recommended by the American Diabetes Association [ADA][13]). Even in the hands of highly specialized endocrinologists, attaining and sustaining optimal glycemic control in many patients remains a daunting task.

There are several physiological explanations for the failure to achieve optimal glycemic control with insulin therapy even in the ideal clinical setting. In healthy subjects, normal glucose homeostasis is achieved by a complex interplay of several glucoregulatory hormones, including the β-cell hormones insulin and amylin, the α-cell hormone glucagon, and a host of gut-derived hormones including the potent insulinotropic incretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP).[14] This becomes most apparent in the postprandial period, when these hormones collectively interact in a precise manner to regulate the rapid and dramatic changes in glucose that need to occur in order to accommodate the sudden and marked influx of nutrients into the circulation.[15] It is well-established that several, if not all, of these hormones are abnormally regulated in the diabetic state, which raises the important question of whether it is realistic to expect that near-normalization of glycemia can be routinely and easily achieved in most patients with exogenous insulin replacement alone.

IN BRIEF

Many insulin-treated diabetic patients still fail to achieve optimal glycemic control and continue to experience problems with hypoglycemia, weight gain, and postprandial hyperglycemia. Adjunctive therapy with pramlintide, a synthetic analog of the human amylin hormone, facilitates a significant improvement of postprandial and overall glycemic control in patients with either type 1 or type 2 diabetes without an increased risk of hypoglycemia or weight gain.

What are the physiological limitations that hinder the restoration of normal postprandial glucose homeostasis in insulin-treated patients with diabetes?

First, the ability to approximate the normal insulin secretory pattern of healthy subjects with exogenous insulin, although much improved with the availability of rapid- and long-acting insulin analogs,[11,12] is still far from optimal. Recent data obtained with a continuous glucose monitoring device have shown that even well-controlled patients with type 1 diabetes treated intensively with CSII have a high prevalence of excessive postprandial glucose excursions.[16,17] This occurs despite administration of rapid-acting insulin analogs at mealtimes.

It should be remembered that subcutaneous insulin delivery presents a compartmental mismatch of insulin in the peripheral and portal circulation. In nondiabetic subjects, insulin is secreted into the portal vein, and as a result, the liver is exposed to two- to fourfold higher insulin concentrations than are the peripheral tissues. In diabetic patients treated with subcutaneous insulin injections, the periphery is exposed to higher insulin concentrations than is the liver. This mismatch becomes most important in the postprandial period, when portal

hypoinsulinemia results in an inability to appropriately suppress hepatic glucose production, thereby favoring postprandial hyperglycemia.[18–21]

Efforts to reduce excessive postprandial peaks by increasing the dose of subcutaneous insulin at mealtime often produce peripheral hyperinsulinemia, which in turn predisposes one to hypoglycemia several hours later. The presence of sustained peripheral hyperinsulinemia may contribute to the considerable weight gain that is so often seen with intensification of insulin therapy.[3,6,9,10]

Secondly, people with either type 1 or type 2 diabetes often manifest with hyperglucagonemia, particularly in the postprandial period when glucagon secretion is normally suppressed.[18–21] Although it was proposed more than three decades ago that diabetes is a state not only of insulin deficiency, but also of glucagon excess (the "bihormonal hypothesis" of diabetes),[22] this notion has not received wide clinical recognition. This is in part because therapeutic tools to correct this abnormality are lacking. Exogenous insulin, even when injected intravenously, does not correct the postprandial rise in glucagon in patients with diabetes.[22]

At present, glucagon is widely known for its use as a treatment for hypoglycemia, particularly in patients with long-standing type 1 diabetes who have lost their glucagon counterregulatory response to hypoglycemia. The fact that even these patients often show postprandial hyperglucagonemia illustrates the two aspects of glucagon pathophysiology in the diabetic state. During the postprandial period, an abnormal rise in glucagon in the portal vein will further offset the already inadequate effect of subcutaneously administered insulin on the liver, further contributing to excessive hepatic glucose production and postprandial hyperglycemia.

A third factor that may influence the success of interventions to improve postprandial glycemic control, and one which is now receiving increasing attention, is the contribution of the gastrointestinal tract to glucoregulatory function. In both healthy subjects and patients with diabetes, the rate at which nutrients are passed from the stomach into the small intestine (i.e., gastric emptying rate) for complete digestion and absorption is a key determinant of the early glucose excursion in the postprandial period.[23] The more rapid the rate of gastric emptying and, hence, the influx of meal-derived glucose into the circulation, the more difficult it is to control the postprandial glucose excursion with exogenous insulin. It is therefore not surprising that, in nondiabetic people, this important glucoregulatory step is tightly regulated by several hormones, including amylin, cholecystokinin (CCK), and the incretins GLP-1 and GIP.

Amylin is a second β-cell hormone that is normally co-secreted with insulin in response to meals and complements the effects of insulin in postprandial glucose control.[24–26] The fact that amylin is deficient in insulin-treated patients with either type 1 or type 2 diabetes has opened a new perspective on the consequences of β-cell destruction (type 1) and dysfunction (type 2) in diabetes. There is a need to consider adopting a less insulinocentric and more multihormonal perspective on diabetes to find ways to further improve glycemic control. This review provides an update on amylin physiology and on the potential utility of pramlintide (Symlin), a synthetic amylin analog, as a novel, physiological approach to improve glycemic control in patients with insulin-requiring diabetes.

Amylin: A Second Glucoregulatory β-Cell Hormone

Amylin is a 37–amino acid peptide that is almost exclusively expressed within pancreatic β-cells, where it is co-packaged with insulin in secretory granules (Figure 1).[24–26] Consequently, amylin is normally co-secreted with insulin, and the plasma concentrations of the two hormones display a similar diurnal pattern of low fasting levels and rapid and robust increases in response to meals (Figure 2A).[15,27–29]

As might be expected, because of the co-localization of both hormones within β-cells, patients with type 1 diabetes have an absolute deficiency of both insulin and amylin, whereas patients with type 2 diabetes have a relative deficiency of both hormones, including a markedly impaired amylin and insulin response to meals (Figure 2B).[15,28,29] These findings have led to questions of whether amylin deficiency contributes to the metabolic derangements in patients with type 1 or type 2 diabetes and, if so, whether amylin replacement might convey clinical benefit when used in conjunction with insulin replacement.

Extensive studies with amylin and amylin antagonists in rodents and with pramlintide in patients with type 1 or type 2 diabetes have provided a solid

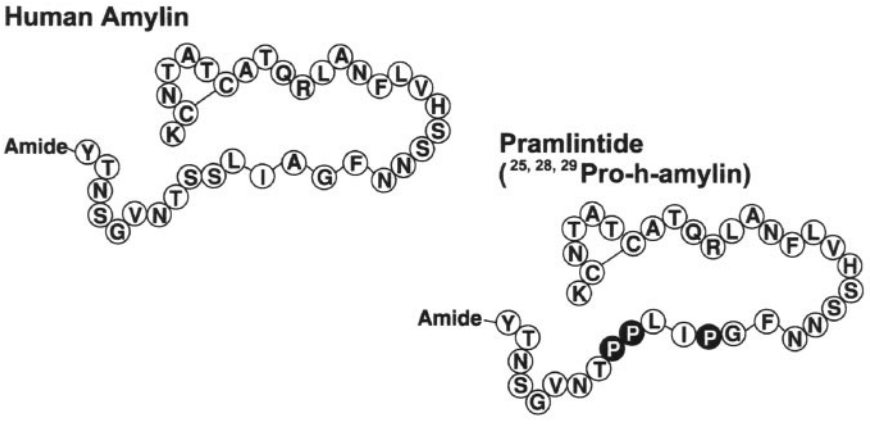

Figure 1. Amino acid sequences of human amylin and the synthetic amylin analog pramlintide.

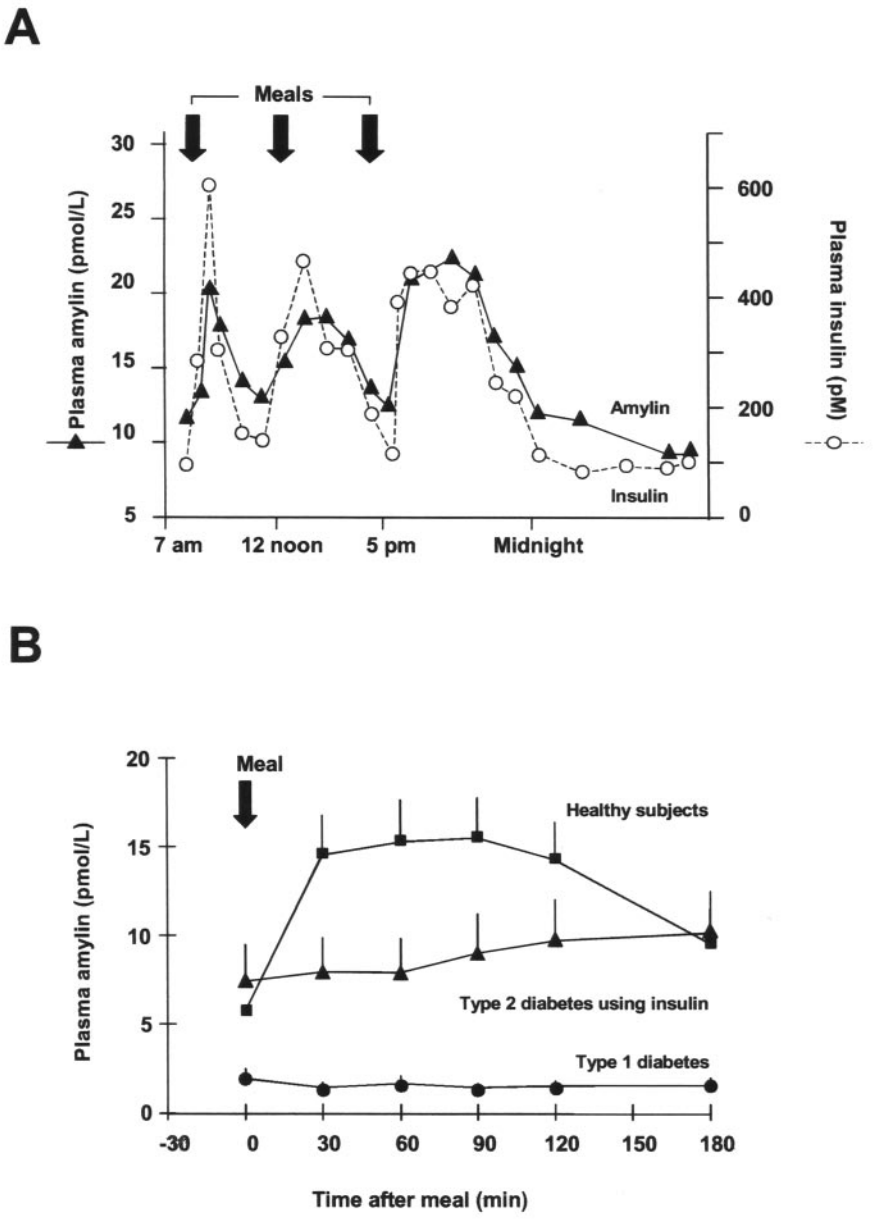

Figure 2. (A) Twenty-four-hour plasma profiles of insulin and amylin in healthy subjects. Insulin and amylin have similar diurnal profiles, with low basal levels and robust increases in plasma glucose after major meals. Adapted from ref. 28. (B) Mean amylin (standard error) plasma concentration versus time after a liquid Sustacal meal. Amylin response in patients with type 1 or type 2 diabetes is demonstrated after a liquid Sustacal meal. Amylin is absent in patients with type 1 diabetes, and amylin secretion is markedly impaired in insulin-requiring patients with type 2 diabetes. Adapted from ref. 29.

understanding of the role of amylin in glucose homeostasis. Preclinical data indicate that amylin acts as a neuroendocrine hormone that complements the actions of insulin in postprandial glucose homeostasis via several mechanisms. These include a suppression of postprandial glucagon secretion and a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption. The net effect of these actions is to mitigate the influx of endogenous (liver-derived) and exogenous (meal-derived) glucose into the circulation and thus to better match the rate of insulin-mediated glucose clearance from the circulation (Figure 3).

Pramlintide: A Synthetic Analog of Human Amylin

Human amylin is rather insoluble and has a propensity to self-aggregate, making it difficult to use the native peptide therapeutically. To overcome this, a soluble, non-aggregating, equipotent analog of human amylin, pramlintide, was developed (Figure 1).[30,31] Over the past decade, pramlintide has been investigated as a means of amylin replacement in patients with insulin-requiring diabetes. Pramlintide is administered by subcutaneous injection before major meals. Pharmacokinetics studies have shown that pramlintide doses of 30 μg and 60 μg in patients with type 1 diabetes and of 120 μg in patients with type 2 diabetes produce plasma pramlintide concentrations that approximate physiological postprandial plasma amylin concentrations in healthy subjects. Following a single subcutaneous injection of pramlintide, plasma concentrations peak at ~20 minutes, regardless of dose, then decline over the subsequent 3 hours. Pramlintide undergoes little or no hepatic metabolism and is cleared mainly via the kidneys, with a plasma half-life of ~50 minutes.[15]

Pramlintide Reduces Postprandial Glucose Excursions

Short-term, placebo-controlled, crossover studies in insulin-treated patients with either type 1 or type 2 diabetes have shown that subcutaneous injection of pramlintide before a mixed meal results in a substantial reduction in the subsequent postprandial glucose excursion (Figure 4, A and B).[32–37] Of note, pramlintide almost entirely prevents the initial surge in plasma glucose concentrations within the first 30–60 minutes after the meal, thereby effectively limiting or even preventing postprandial hyperglycemia. This marked effect

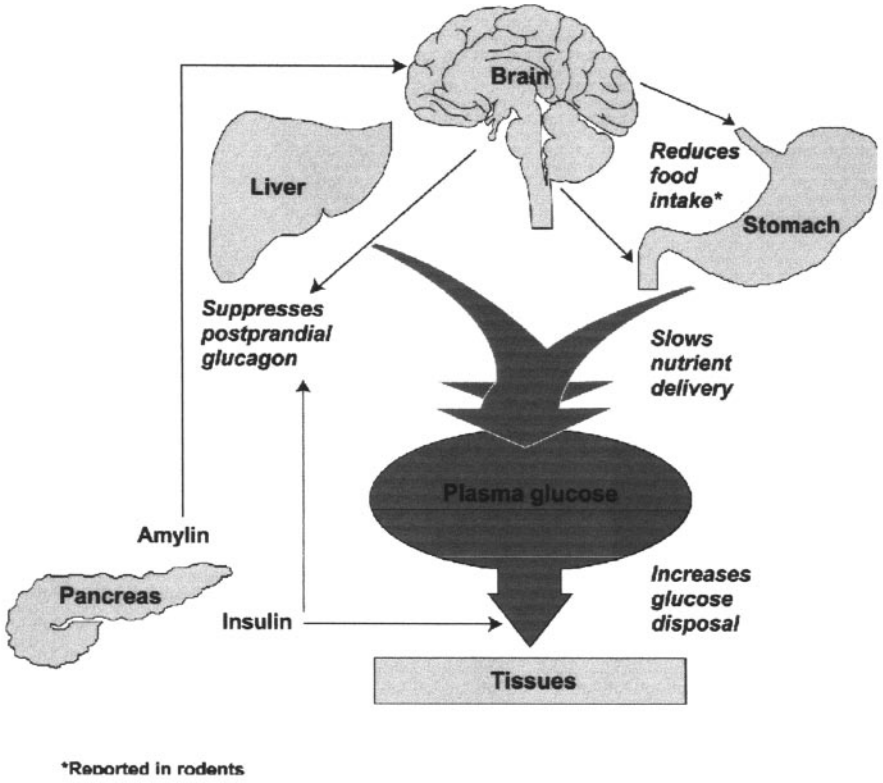

Figure 3. Proposed model of amylin and insulin action in postprandial glucose homeostasis. Insulin is the major hormonal regulator of glucose disposal. Preclinical and clinical studies indicate that amylin complements the effects of insulin by regulating the rate of glucose inflow to the bloodstream.

on the postprandial glucose profile can be achieved with doses of pramlintide that produce plasma concentrations that approximate the postprandial amylin response in healthy subjects, suggesting that the postprandial glucose-lowering effect is a physiological result of amylin replacement and not simply a pharmacological (supra-physiological) effect.

The potential mechanism of action underlying pramlintide's effect on postprandial glucose control has been studied in detail. An important action is its effect on postprandial glucagon secretion. Glucagon is the main stimulus for hepatic glucose production. Many patients with either type 1 or type 2 diabetes have an inadequate suppression, or even an inappropriate increase, in glucagon secretion, whereas the glucagon secretory response to hypoglycemia is usually impaired in patients with long-existing type 1 diabetes.[18–21] Several crossover studies have shown that when patients with diabetes inject placebo with their insulin at mealtime, they have an abnormal rise in plasma glucagon concentration. In contrast, when those patients received pramlintide in addition to their usual insulin dose, the postprandial rise in glucagon was almost entirely prevented.[38,39]

An important characteristic of the glucagonostatic effect of pramlintide is that it is overridden in the presence of hypoglycemia. A study in patients with type 1 diabetes found that pramlintide does not suppress glucagon concentrations in response to insulin-induced hypoglycemia,[40] and similar observations have been made in rodents treated with amylin.[41]

Another important mechanism of action of pramlintide is its effect on gastric emptying. Studies of pramlintide in patients with diabetes have shown that it slows the rate of nutrient delivery from the stomach to the small intestine with both solid and liquid meals.[42,43] At the doses of pramlintide used in long-term clinical trials, the half-gastric emptying time was prolonged by ~90 minutes. Thus, pramlintide administration slows gastric emptying to effectively limit postprandial glucose excursions while still allowing complete emptying of the stomach between meals.[42–44]

Experimental investigations in rodents indicate that the effects of amylin, and by inference pramlintide, on nutrient delivery are mediated via a central pathway that involves the area postrema and visceral efferents of the vagus nerve. The area postrema in the brainstem contains a high density of amylin binding sites,[45–48] and is exposed to changes in plasma amylin and glucose concentrations because it does not have a blood-brain barrier. Selective lesioning of the area postrema and/or bilateral vagotomy abolishes the effect of amylin on gastric emptying,[49,50] demonstrating the importance of this central pathway in mediating amylin's physiological functions. An important characteristic of the effect of amylin to slow gastric emptying is that this action is dependent on the ambient glucose level, i.e., it is overridden in the presence of hypoglycemia.[51]

Pramlintide Improves Long-Term Glycemic and Weight Control

The effects of pramlintide therapy on long-term glycemic control in patients with insulin-requiring type 1 or type 2 diabetes have been investigated in four double-blind, placebo-controlled, parallel-group, multicenter studies of 12 months' duration.[52–55] In all of these studies, subcutaneous injections of pramlintide were administered in addition to the patients' existing insulin regimens (add-on design).

These studies consistently demonstrated that the addition of pramlintide to pre-existing insulin therapy improved overall glycemic control in patients with either type 1 or type 2 diabetes, as evidenced by significant reductions in A1C

of ~0.5–1.0% from baseline and ~0.3–0.5% compared to placebo (Figure 5, A and B).[52,53] Furthermore, the proportion of patients who were able to achieve ADA glycemic targets (A1C <7%) was two- to threefold greater with pramlintide plus insulin than with insulin alone. Importantly, the improvements in glycemic control seen in the pramlintide-treated patients were generally achieved without increases in insulin dosage over the duration of the study. On the contrary, total daily insulin doses were generally lower among pramlintide- compared to placebo-treated patients, a finding consistent with the effects of pramlintide being complementary to those of insulin.

Of even greater clinical significance is the consistent finding in these studies that the improved glycemic control observed in patients who received pramlintide in addition to their usual insulin regimen was not associated with weight gain. Conversely, the reductions in A1C with pramlintide therapy were generally associated with a mean weight loss (Figure 5, C and D).[52,53]

Stratification by baseline body mass index (BMI) revealed that pramlintide tended to prevent weight gain in patients who were lean at study entry and induced increasing amounts of weight loss in overweight and obese patients. This weight loss averaged 1.6 kg in patients with type 1 diabetes with a BMI >27 kg/m^2 and 2.4 kg in patients with type 2 diabetes with a BMI >35 kg/m^2 after treatment with pramlintide for 26 weeks.[56] Pooled analyses of data from the long-term trials in patients with type 1 or type 2 diabetes showed that twice the number of pramlintide- than placebo-treated patients achieved a simultaneous reduction in both A1C and body weight.[57,58]

The long-term improvement of glycemic control with pramlintide was not associated with an increase in the overall event rate of severe hypoglycemia, as is often seen when glycemic control is improved by intensification of insulin therapy.[5,8] Although

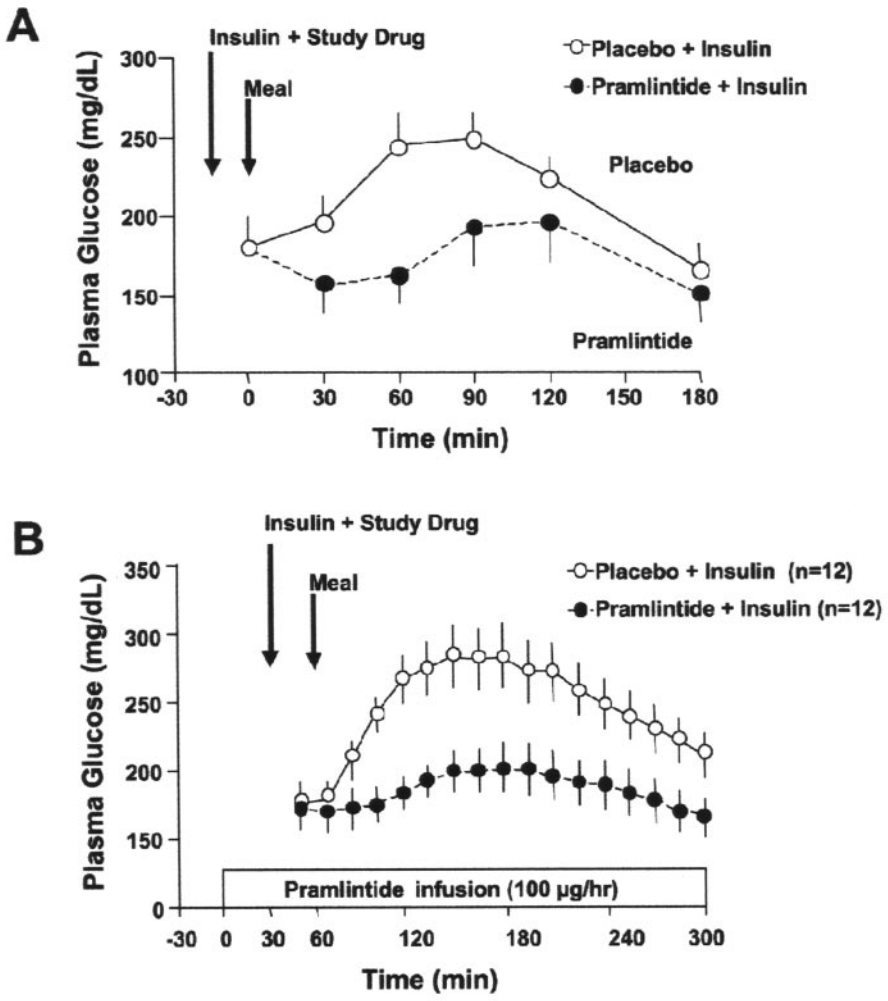

Figure 4. (A) Mean glucose concentrations (standard error) over a 3-hour period in 21 placebo- and 15 pramlintide-treated patients with type 1 diabetes treated for 14 days with placebo + regular insulin or 30 µg pramlintide + regular insulin before meals. Adapted from ref. 33. (B) Changes in mean plasma glucose concentrations during a 5-hour intraveneous infusion of pramlintide or placebo as an adjunct to mealtime injections of regular insulin in patients with type 2 diabetes. Adapted from ref. 36.

the greater reduction in A1C with pramlintide was sustained over the long term, it was during the first 4 weeks that pramlintide-treated patients had a transient increase in severe hypoglycemic episodes compared to placebo-treated patients.[52–55]

It is important to note that this transient increase occurred within the context of double-blind clinical trials, which discouraged patients from changing their insulin dose in order to fully demonstrate the pramlintide treatment effect. In routine clinical practice, this risk should be manageable with regular blood-glucose monitoring and appropriate insulin dose adjustments, such as a temporary reduction of mealtime insulin doses during initiation of pramlintide treatment. This approach is being formally tested in trials that are underway.

Beyond the first 4 weeks, the rate of severe hypoglycemia was not increased in pramlintide-treated patients, despite the sustained reduction in A1C. This is consistent with pramlintide being an

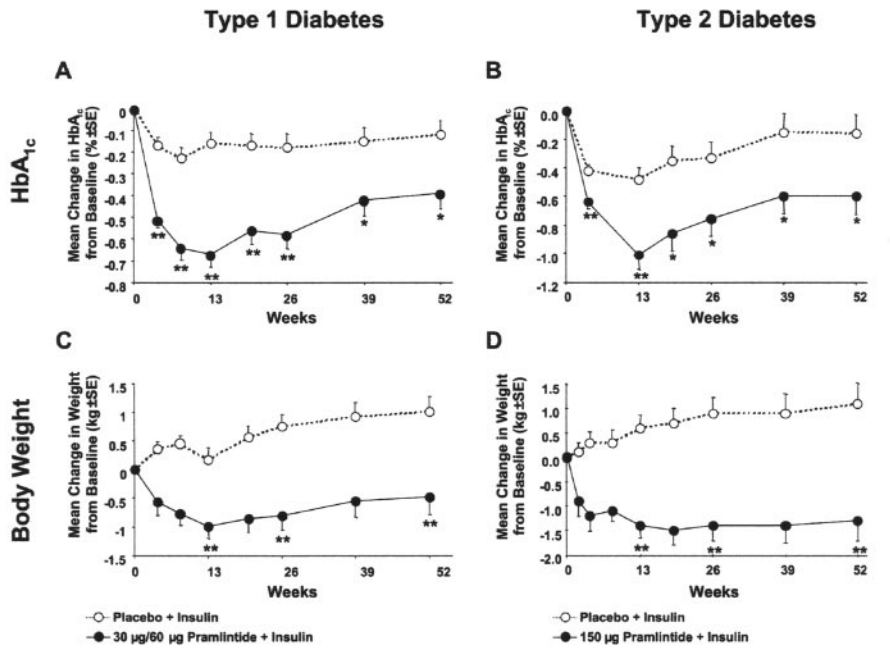

Figure 5. Mean changes (standard error) from baseline in A1C (A and B) and body weight (C and D) for patients with type 1 (A and C) or type 2 (B and D) diabetes treated with placebo + insulin or pramlintide + insulin. From ref. 52 and ref. 53. Statistical significance is denoted by * (P < 0.05) and ** (P < 0.001). In both types of diabetes, addition of pramlintide to existing insulin therapy led to significant and sustained reductions in both A1C and body weight.

anti-hyperglycemic agent, which, unlike insulin, does not cause hypoglycemia in and of itself, even when administered at very high doses.[59]

Tolerability

Pramlintide treatment was generally well-tolerated. No evidence of cardiac, hepatic, or renal toxicity; changes in serum lipid parameters; or clinically relevant changes in laboratory tests, vital signs, electrocardiograms, or abnormal findings upon physical examinations have been found in patients treated with pramlintide.[52–55]

The most common adverse events reported with pramlintide treatment were nausea, anorexia (feeling of fullness), and vomiting. These symptoms were generally more common in patients with type 1 than in those with type 2 diabetes. They occurred early after initiation of therapy and were mostly of mild-to-moderate intensity, dose-dependent, and resolved over time. This suggests that they may be manageable by gradual dose titration when introducing pramlintide therapy.[15] This hypothesis is being formally tested.

Conclusion

Although the past decade has brought major advances in insulin pharmacology and delivery that have greatly improved insulin therapy for both type 1 and type 2 diabetes, many, if not most, insulin-treated patients are still unable to attain and sustain optimal glycemic control. Recurrent hypoglycemia, weight gain, and an inability to control postprandial glucose excursions are among the many barriers of insulin therapy that continue to trouble patients and hinder their efforts to attain glycemic targets. Clearly, novel therapeutic tools that could be used as an adjunct to insulin therapy to achieve a further improvement of glycemic control without increasing the risk of hypoglycemia and weight gain would represent valuable, much needed additions to our therapeutic armamentarium.

Normal glucose homeostasis in healthy subjects is achieved by a complex interplay of several islet and gut hormones, including insulin, amylin, glucagon, and incretins. Since the diabetic state is manifested by abnormalities in several, if not all, of these hormones, hormonal targets other than insulin should be explored as physiological approaches to improve diabetes therapy.

Correction of amylin deficiency in patients with advanced β-cell failure using the amylin analog pramlintide as an adjunctive therapy to insulin has been shown to improve postprandial and overall glycemic control in patients with either type 1 or type 2 diabetes without increasing the risk of hypoglycemia or weight gain. For patients with type 1 diabetes, pramlintide represents the first agent in 80 years that has been shown to improve long-term glycemic control above and beyond insulin. For insulin-treated patients with type 2 diabetes, who have typically advanced to a stage where they have exhausted other therapeutic options, pramlintide may become an important addition to the therapeutic armamentarium, especially with its beneficial effects on postprandial glucose control and body weight.

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