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Exenatide and pramlintide: New glucose-lowering agents for treating diabetes mellitus

ABSTRACT

Insulin is not the only hormone that regulates plasma glucose levels. Glucagon-like peptide 1 (GLP-1), produced in the small intestine, and amylin, produced by beta cells in the pancreas, also have glucose-lowering effects. Synthetic analogues of these hormones are now available for clinical use.

KEY POINTS

Exenatide, an analogue of GLP-1, is approved for patients with type 2 diabetes who are also being treated with a sulfonylurea, metformin, or both.

Pramlintide, an analogue of amylin, is approved for patients with either type 1 or type 2 diabetes being treated with insulin.

Both drugs are given subcutaneously before meals.

Both drugs are associated with a modest weight loss.

Nausea is the most common side effect of both drugs.

Exenatide, which stimulates insulin secretion, may cause hypoglycemia when it is given with sulfonylurea drugs (which also stimulate insulin secretion) but not with metformin alone.

*The author has indicated that he serves on an advisory committee to develop educational materials for the Amylin/Lilly Synergy partnership.

TWO NEW DRUGS for treating diabetes mellitus have been approved in the past year, both of them based on native hormones that are deficient in patients with diabetes:

- Exenatide (Byetta), an analogue of the gut hormone glucagon-like peptide 1 (GLP-1); and
- Pramlintide (Symlin), a modified version of the pancreatic hormone amylin.

This article describes the effects of the two native hormones and their synthetic analogues. Clinical studies of the glucose-lowering effects of these analogues and their proposed use in the management of hyperglycemia in diabetes mellitus will be reviewed.

GLP-1: A GUT HORMONE

Researchers first suspected in the 1960s that mechanisms in the gut contribute to lowering glucose levels when they observed that plasma insulin levels rose higher in response to a glucose load given enterally than to a comparable load given intravenously. Furthermore, patients with partial insulin deficiency needed higher insulin doses to cover calories given parenterally than for a comparable number of calories given enterally.

This "incretin effect" suggested that factors in the gut stimulate insulin secretion or might facilitate glucose-lowering independently of insulin. The search for an "incretin" resulted in the discovery of a peptide secreted by the L cells of the small intestine, called

Effect of exenatide on hemoglobin A_{1c} in clinical studies

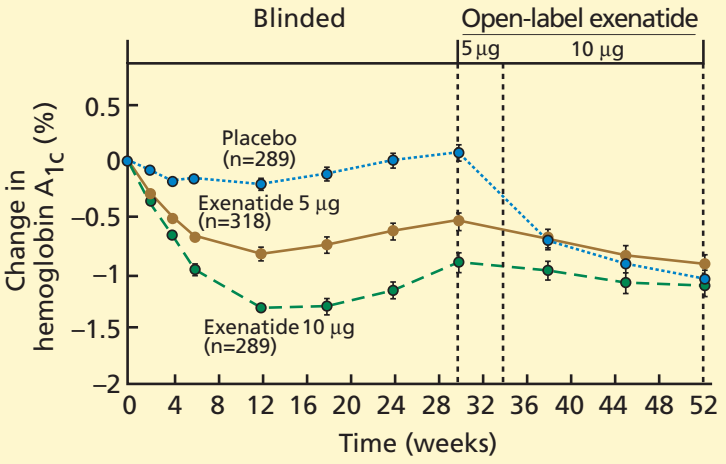

FIGURE 1. Effect of exenatide on hemoglobin A_{1c} in clinical studies. Before treatment, the mean hemoglobin A_{1c} level was 8.5 ± 1.1% in the placebo group, 8.4 ± 1.1% in the exenatide 5 µg group, and 8.5 ± 1.1% in the exenatide 10 µg group. All doses were given twice a day. Values are mean ± standard error of the mean.

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glucagon-like peptide 1 (GLP-1).[1] In addition to a glucose-dependent, insulin-stimulating effect, GLP-1 also suppresses glucagon and delays gastric emptying.

In healthy people, plasma insulin levels rise to a peak very quickly after eating (first-phase insulin secretion), followed by another peak and then decline to a plateau over several hours (the second phase). At the same time, the pancreas curtails its production of glucagon, the hormone that mobilizes glucose from the liver.

In contrast, people with diabetes have loss of first-phase insulin secretion, with progressive loss of total insulin production. They also have postprandial glucagon concentrations that fail to be suppressed and are thus inappropriately high—sometimes even higher than in the fasting state.

Interestingly, people with type 2 diabetes have lower levels of GLP-1 than people without diabetes, and infusions of GLP-1 correct these metabolic defects, increasing glucose-stimulated insulin production and suppressing postprandial glucagon production.

EXENATIDE: A GLP-1 ANALOGUE

Native GLP-1 has a very short half-life, measured in minutes; therefore, a drug that is exactly the same as native GLP-1 would be suitable for clinical use only if given by continuous infusion. This short half-life is a result of cleavage of the GLP-1 molecule at its C-terminal site by an enzyme called dipeptidyl dipeptidase IV (DPP-IV).

There are basically two strategies for exploiting the GLP-1 system clinically: build a longer-acting analogue of GLP-1 that resists metabolism by DPP-IV, or block DPP-IV with a molecule that competitively binds to it. Both strategies have been studied.

Exenatide, a parenteral drug, is a long-acting analogue of GLP-1. Based on a GLP-1-like hormone found in the desert lizard *Heloderma suspectum* (commonly called the gila monster), this molecule has multiple amino acids that are identical to those in the same positions in human GLP-1 but it has a modification in its C-terminal end that makes it resistant to DPP-IV-mediated degradation.

In addition, several oral DPP-IV inhibitors that increase the half-life of native GLP-1 are undergoing clinical investigation and will likely be available in the next several years.

Clinical studies of exenatide

The immediate effects of exenatide are to increase insulin secretion and suppress glucagon secretion, decreasing both fasting and postprandial glucose concentrations.[2–4]

Most of the information on the use of exenatide in diabetic patients comes from the studies performed to get approval from the US Food and Drug Administration for clinical use.[5–8] These studies were in patients who were already receiving a sulfonylurea, metformin, or both, to which exenatide was added.

Reduction in hemoglobin A_{1c}. In these studies, the mean hemoglobin A_{1c} values at baseline ranged from 8.2% to 8.7% in the various treatment groups. At 30 weeks, these values had fallen by about 0.6% (absolute reduction) with exenatide 5 µg twice a day and by about 0.9% with 10 µg twice a day. In the placebo groups, values rose by 0.1%.

TABLE 1

Mean change in hemoglobin A_{1c} and weight in selected glucose-lowering studies

AGENT	N	DURATION	MEAN ABSOLUTE DECREASE IN HEMOGLOBIN A_{1c} (%)	MEAN CHANGE IN WEIGHT (KG)
Insulin				
DCCT intensive	711	6.5 years	1.5	+9.8
DCCT conventional	730	6.5 years	0.2	+2.4
SDIS intensive	48	7.5 years	2.4	+4.4
SDIS conventional	54	7.5 years	0.9	+1.8
Four other studies	14 to 73	16 to 26 weeks	1.7 to 2.6	+1.9 to +8.7
Sulfonylureas (three studies)	21 to 34	26 to 52 weeks	1.1 to 1.9	+2.8 to +3.6
Meglitinides (three studies)	45 to 179	18 to 52 weeks	0.5 to 1.3	+0.7 to +0.9
Thiazolidinediones (three studies)	76 to 187	26 to 28 weeks	0.9 to 1.5	+2.6 to +3.5
Metformin (three studies)	38 to 143	28 to 29 weeks	0.9 to 1.4	–0.6 to –0.8
Alpha glucosidase inhibitors (three studies)	40 to 973	24 to 52 weeks	0.4 to 0.8	–0.4 to –1.5
Exenatide (three studies)	223 to 446	30 weeks	0.4 to 0.9	–0.9 to –2.8
Pramlintide (four studies)	144 to 243	1 year	0.4 to 0.7	–0.5 to –1.5

DCCT: Diabetes Control and Complications Trial; SDIS: Stockholm Diabetes Intervention Study
Values for combined studies are ranges

ADAPTED FROM PURNELL JQ, WEYER C. WEIGHT EFFECT OF CURRENT AND EXPERIMENTAL DRUGS FOR DIABETES MELLITUS: FROM PROMOTION TO ALLEVIATION OF OBESITY. TREAT ENDOCRINOL 2003; 2:33–47.

These effects were comparable with each of the combinations of medications and appear to have been durable for up to a year in unblinded follow-up studies (FIGURE 1). These improvements are roughly comparable with those achieved with most oral glucose-lowering agents (TABLE 1).

Weight loss. Patients tend to gain weight during treatment with most oral agents or insulin: about 2 kg (4.4 lbs) for every 1% reduction in hemoglobin A_{1c} (reviewed by Purnell and Weyer,[9] TABLE 1). However, more than 80% of patients treated with exenatide lost weight: 3 to 5 lb at 30 weeks and a mean of 8 lb at 1 year (FIGURE 2). Furthermore, they kept the weight off for 2 years (data presented at the American Diabetes Association scientific sessions, 2005). No data are available about longer duration of sustained weight loss or about weight loss in people without diabetes. The weight loss is attributed to the anorectic effect of the medication.

Nausea was the main side effect of exenatide (TABLE 2). Nausea remits over time and does not correlate consistently with weight loss.

Hypoglycemia was more common in patients taking exenatide along with a sulfonylurea drug, but not in those taking exenatide combined with metformin alone (TABLE 2).

The risk of hypoglycemia is not likely to be increased in patients taking exenatide with other oral agents that do not stimulate insulin production, such as thiazolidinediones and alpha glucosidase inhibitors (also known as disaccharide inhibitors), because the effect of GLP-1 on insulin secretion depends on the plasma glucose concentration.

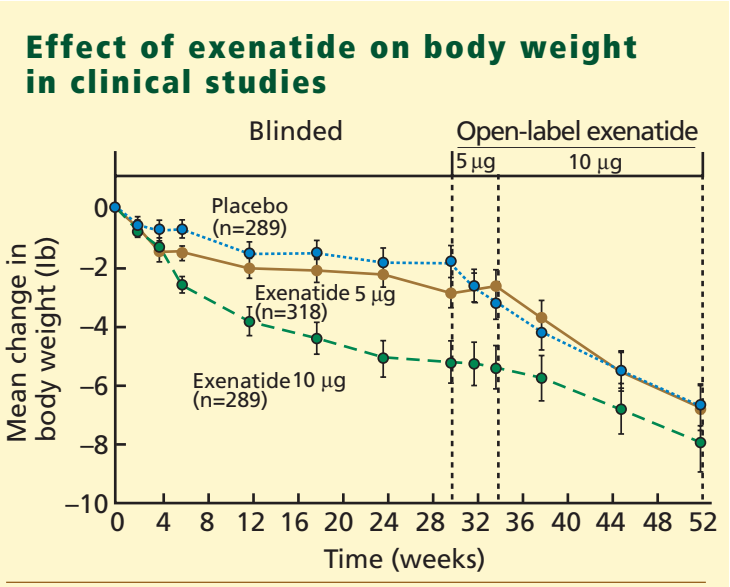

FIGURE 2. Effect of exenatide on body weight during clinical studies. Before treatment, the mean weight was 217.8 ± 41.8 lb in the placebo group, 213.4 ± 44 lb in the exenatide 5 µg group, and 215.6 ± 44 lb in the exenatide 10 µg group. All doses were given twice a day. Values are mean ± standard error of the mean.

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TABLE 2

Side effects of exenatide in three pivotal studies

SIDE EFFECT	PLACEBO GROUP (N = 483)	EXENATIDE GROUP (N = 963)
Nausea	18%	44%
Vomiting	4%	13%
Diarrhea	6%	13%
Hypoglycemia		
Overall	8%	20%*
With exenatide + metformin only	5%	5%

*Including one episode of severe hypoglycemia in a sulfonylurea-treated patient

DATA FROM BUSE JB, HENRY RR, HAN J, ET AL. EFFECTS OF EXENATIDE (EXENDIN-4) ON GLYCEMIC CONTROL OVER 30 WEEKS IN SULFONYLUREA-TREATED PATIENTS WITH TYPE 2 DIABETES. DIABETES CARE 2004; 27:2628–2635; KENDALL DM, RIDDLE MC, ROSENSTOCK J, ET AL. EFFECTS OF EXENATIDE (EXENDIN-4) ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH METFORMIN AND A SULFONYLUREA. DIABETES CARE 2005; 28:1083–1091; AND DEFRONZO RA, RATNER RE, HAN J, ET AL. EFFECTS OF EXENATIDE (EXENDIN-4) ON GLYCEMIC CONTROL AND WEIGHT OVER 30 WEEKS IN METFORMIN-TREATED PATIENTS WITH TYPE 2 DIABETES. DIABETES CARE 2005; 28:1092–1100.

Who should receive exenatide?

Exenatide is currently approved for use only in combination with a sulfonylurea, metformin, or both, in patients with type 2 diabetes mellitus (TABLE 3). In view of its effect on weight, the typical patient for whom it should be considered is obese, with elevated glucose concentrations in spite of therapy with these agents.

Because exenatide stimulates insulin secretion, its glucose-lowering effects should be comparable if it is used as monotherapy, although we do not yet have any data about this from clinical trials.

I believe exenatide will also be effective in combination with thiazolidinediones (pioglitazone, rosiglitazone), short-acting insulin secretagogues (nateglinide, repaglinide), alpha glucosidase inhibitors (acarbose, miglitol), or combinations of these oral agents. In fact, I believe it should be considered for use in patients who are already on three-drug or four-drug oral agent combinations. Studies are under way to assess its efficacy with thiazolidinediones and to determine whether it attenuates the weight gain commonly seen with thiazolidinedione use.

Using exenatide in place of insulin secretagogues has appeal because hypoglycemia probably will not be a serious concern. The advantages of exenatide (less risk of hypoglycemia and weight loss vs weight gain with the insulin secretagogues) need to be balanced against its disadvantages, eg, the need for injections and issues of cost (from $150 to $200 per month) and insurance coverage.

It is not yet clear whether exenatide will be effective in patients who are already on insulin therapy, whose insulin secretory capacity is already diminished: patients need to have some residual insulin secretion for exenatide to have an insulin-mediated glucose-lowering effect.

Furthermore, hypoglycemia occurs when exenatide is used with sulfonylureas and obviously could occur when it is used with insulin. Exenatide used as monotherapy or with thiazolidinediones or alpha glucosidase inhibitors is not likely to be associated with much risk for hypoglycemia. Because alpha glucosidase inhibitor use is associated with nausea, exenatide use with these agents may be associated with more nausea.

TABLE 3

Possible uses of exenatide

REGIMEN	COMMENTS
Approved uses	
Combined with metformin	Decreases hemoglobin A_{1c}, weight[7,8]
Combined with a sulfonylurea	Decreases hemoglobin A_{1c}, weight[7,8] Increases risk of hypoglycemia
Combined with metformin plus a sulfonylurea	Decreases hemoglobin A , weight[7]
Nonapproved uses	
Combined with a thiazolidinedione	Studies in progress
Combined with an alpha glucosidase inhibitor	No published studies
Combined with a short-acting insulin secretagogue	No published studies Risk of hypoglycemia should be low
Combined with three or more oral agents	Effects should be additive to all other agents Risk of hypoglycemia with insulin secretagogues
Monotherapy	Effects on glucose, insulin, and glucagon demonstrated in short-term studies Should decrease hemoglobin A_{1c}, weight
Combined with insulin therapy	Studies in progress Risk of hypoglycemia may be higher than with other regimens Glucose-lowering efficacy may be reduced with long-standing diabetes and low endogenous insulin secretory capacity Decreased hemoglobin A_{1c} is uncertain; decreased weight is likely

Exenatide is not approved for use in patients with type 1 diabetes mellitus. It could in theory have favorable effects in adult patients with type 1 diabetes with some residual beta cell function who are obese or who do not suppress glucagon with meals, but we have no data. Such use would not generally be considered to be prudent, especially since there is now an alternative agent (pramlintide, see below) for patients with type 1 diabetes who are receiving insulin.

At present, there are no known significant drug interactions. Relative contraindications include symptomatic gastroparesis. Exenatide is not approved for use in pregnancy.

Dosage and administration

The starting dosage of exenatide is 5 μg subcutaneously twice a day before meals (breakfast and dinner). After 1 month, the dosage is increased to 10 μg twice a day if nausea is not a serious problem.

The drug is available in a pen that delivers 60 fixed doses of either 5 μg or 10 μg—1 month's supply. It is possible to start at the lower dose and give two injections to achieve the higher dose, although progression to the next pen is simpler.

Does exenatide protect beta cells?

Some experiments in rodents suggest that exenatide may slow the natural decline in insulin production or protect against further decline in animals treated with beta cell toxins.[10,11] If these observations are confirmed in human studies, then exenatide may become a first-line therapy in type 2 diabetes mellitus, perhaps in combination with thiazolidinediones, for which similar beta cell protection has been proposed.

Effect of pramlintide on postprandial glucose concentration

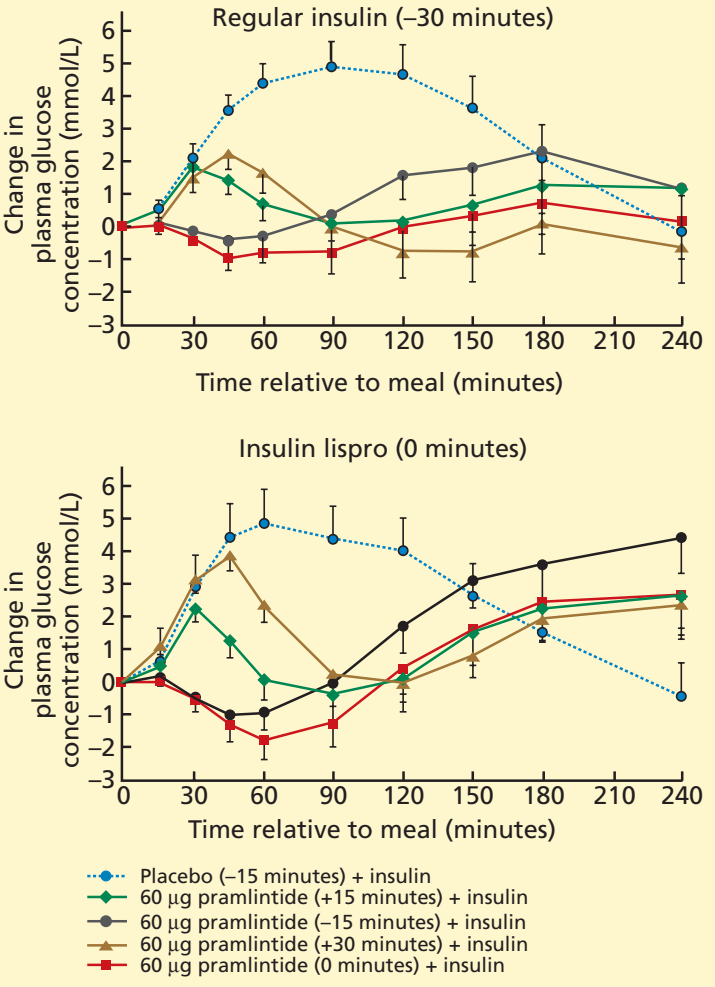

FIGURE 3. Postprandial glucose profiles after a standardized breakfast in type 1 diabetic subjects following injections of regular insulin or insulin lispro plus either placebo or pramlintide 60 µg. Values are mean ± standard error of the mean.

FROM WEYER C, GOTTLIEB A, KIM DD, ET AL. PRAMLINTIDE REDUCES POSTPRANDIAL GLUCOSE EXCURSIONS WHEN ADDED TO REGULAR INSULIN OR INSULIN LISPRO IN SUBJECTS WITH TYPE 1 DIABETES. DIABETES CARE 2003; 26:3074–3079. COPYRIGHT 2003 AMERICAN DIABETES ASSOCIATION. REPRINTED WITH PERMISSION FROM THE AMERICAN DIABETES ASSOCIATION.

AMYLIN: A PANCREATIC HORMONE

In the late 1800s, von Mering and Minkowski studied pancreatectomized animals and inferred that there is a glucose-lowering factor in the pancreas. This factor was difficult to isolate because of pancreatic enzymes that degrade proteins. Nevertheless, Barron observed that stones in the pancreatic duct resulted in acinar tissue atrophy, and Banting conducted experiments in which he ligated the duct to cause acinar tissue atrophy and discovered insulin in pancreatic homogenates (reviewed by Bliss[12]).

Subsequently, it became apparent that there were secretory granules in the pancreatic islets that did not contain insulin. This observation resulted in the characterization of another pancreatic peptide, which became known as amylin.

Amylin, produced by the beta cells, is secreted along with insulin in response to meals. Amylin concentrations are deficient in patients with type 1 diabetes who are also deficient in insulin.

PRAMLINTIDE: AN AMYLIN ANALOGUE

Native amylin is "glue-like" and not amenable to clinical use. However, substituting proline for other amino acids at several key sites yielded a molecule called pramlintide.

Pramlintide has glucose-lowering effects that were independent of and additive to insulin action in animal and human studies (FIGURE 3). The exact mechanism is not well characterized, but glucagon suppression has been demonstrated in both type 1 and type 2 diabetes mellitus. Delaying gastric emptying may also play a role.

Clinical studies of pramlintide

In clinical studies, pramlintide improved prandial glucose control when added to insulin therapy in patients with type 1 and type 2 diabetes.[13–18] In addition, pramlintide use was associated with weight loss.[19]

Whitehouse et al[15] reported on 480 patients with type 1 diabetes treated with insulin and either pramlintide 30 µg four times a day or placebo. At 13 weeks, hemoglobin A_{1c} levels had fallen by a mean of 0.67% (absolute reduction) in the pramlintide group vs 0.16% in the placebo group ($P < .0001$). This effect was more modest over time: at 52 weeks, the mean decline from baseline was 0.39% in the pramlintide group vs 0.12% in the placebo group ($P = .0071$). This effect appeared to be durable in the 236

subjects who participated in the open-label extension for an additional year.

Patients also lost weight with pramlintide therapy, nearly 1 kg at 13 weeks, while they gained weight with insulin therapy alone. The weight loss did not appear to be durable, as the original pramlintide group regained weight during the extended follow-up.

Weyer et al[16] evaluated the effects of pramlintide 60 μg mixed with regular or lispro insulin and showed a reduction in postprandial glucose excursions, especially in patients who took the pramlintide 15 minutes before meals or with meals (**FIGURE 3**). However, pramlintide is not yet approved to be mixed with insulin before administration.

Similar reductions in hemoglobin A_{1c} and weight have been reported in insulin-treated patients with type 2 diabetes who received various doses of pramlintide (60 μg three times a day, 90 μg three times a day, or 120 μg twice a day).[17,19] In these studies, nausea (including severe nausea) was more than twice as likely to occur with pramlintide than with placebo. Nausea did not affect study drop-out rates, however. Weight loss did not correlate well with reported nausea. However, the absolute mean change in weight was greater in patients with higher body mass indices.[15,19] The risk of hypoglycemia was similar in both groups. Insulin requirements in these studies were about 7% to 8% lower in pramlintide-treated patients.[15]

In each of these studies, pramlintide was given by an injection that was separate from the insulin injection. Small studies comparing the effects of pramlintide given separately or combined with insulin suggest that combination with insulin does not adversely alter the effects of pramlintide on blood glucose.[20]

Who should receive pramlintide?

Pramlintide is indicated as an adjunct treatment in patients with either type 1 or type 2 diabetes who use mealtime insulin therapy and have not achieved desired glucose control despite optimum insulin therapy.

However, pramlintide's use in clinical practice will likely be limited to small segments of the diabetic population. At present, it would seem to have the greatest benefit in patients with type 1 diabetes who are obese. Whether its favorable effects on postprandial glycemic excursions will reduce the risk for complications of diabetes cannot be answered at present.

Although pramlintide has also shown favorable effects in patients with type 2 diabetes, its effects on weight are more modest than those of exenatide, which will likely have broader use in type 2 diabetes. It is conceivable that pramlintide may have a greater role in type 2 diabetic patients who have long-standing disease and are more insulin-deficient, as exenatide requires beta cell function to achieve its glucose-lowering effects, whereas pramlintide does not.

In summary, pramlintide has demonstrated efficacy in both type 1 and type 2 diabetes mellitus. It can be used in patients who have low endogenous insulin secretion, and its effects are additive to those of insulin. Patients for whom pramlintide seems most appropriate are those who are insulin-deficient and in whom weight loss (or avoiding weight gain) is desirable. However, its effect on glycemic control is modest, and nausea is common. The fact that it is injectable poses a barrier to its use. As with exenatide, starting at low doses and increasing as tolerated is advisable.

Pramlintide will probably be used more in type 1 than type 2 diabetes

Pramlintide should not be used in patients with symptomatic gastroparesis. The risk for hypoglycemia may be increased with pramlintide use. Expense will be a consideration for patients. There are no known long-term adverse effects, although the drug is not approved for use in pregnancy.

Dosage and administration

When starting pramlintide therapy, the patient's preprandial insulin dose may need to be reduced. In patients with marked elevations of postprandial glucose, no reduction of insulin may be necessary, but in patients already in tight glucose control, prandial insulin may need to be reduced by 50%.

In patients with type 1 diabetes, the initial dosage of pramlintide is 15 μg (2.5 units in a U-100 insulin syringe) subcutaneously before meals, with frequent monitoring of blood glucose levels. If the patient experiences no nausea for 3 days, the dosage can be increased in 15-μg increments as tolerated to

a target dose of 30 or 60 μg.

In patients with type 2 diabetes, the starting dose is 60 μg before meals, which can be increased to 120 μg if there has been no nausea for 3 to 7 days.

In either type of diabetes, the insulin dose is adjusted to achieve optimal glycemic control after the pramlintide dosage is stable.

Symlin is available in vial form, but since many injectable compounds for diabetes come in pen form, it is reasonable to assume this delivery device may be available in the future.

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CORRECTION

Primary hyperparathyroidism

(DECEMBER 2005)

The article "Primary hyperparathyroidism: 7,000 years of progress" by Dr. Michael A. Levine in the December 2005 issue of the *Cleveland Clinic Journal of Medicine* (Cleve Clin J Med 2005; 72:1084–1098) contained a typographical error. On page 1095, in the discussion of familial hypocalciuric hypercalcemia, the defect is in fact due to an inactivating mutation in the gene encoding the calcium-sensing receptor (CASR), not an activating mutation as printed. We would like to thank Dr. Paul Sacks, of Phoenix, AZ, for pointing this out.

CME ANSWERS

Answers to the credit test on page 495 of this issue

1 **E** 2 **D** 3 **E** 4 **B** 5 **A** 6 **A** 7 **E** 8 **B** 9 **E** 10 **A** 11 **C** 12 **A** 13 **E** 14 **C**