Primer on Pramlintide, an Amylin Analog

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Primer on Pramlintide, an Amylin Analog

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Purpose

Pramlintide is an injectable synthetic analog of human amylin. It is indicated for patients with type 1 or type 2 diabetes who are taking mealtime insulin but have been unable to achieve desired glucose targets. Pramlintide decreases postprandial glucose by lowering inappropriate postmeal glucagon secretion, slowing gastric emptying, and increasing satiety. As such, pramlintide targets several of the defects commonly seen in patients with diabetes. Given the unique characteristics of this agent in the treatment of diabetes, a practical guide to its use is presented.

Conclusion

Pramlintide treats diabetes with a novel mechanism of action, offering the potential for improved postprandial control and weight loss for patients with type 1 or type 2 diabetes. Providers and diabetes educators should be familiar with the utility of the medication as well as its potential limitations in order to fully educate patients and maximize treatment options for patients with diabetes.

Diabetes education empowers patients to take a more active role in the management of their disease. This article is intended to serve as a resource for health care professionals caring for patients treated with pramlintide, a medication that targets several of the defects commonly seen in patients with diabetes.

Pramlintide acetate (Symlin®, Amylin Pharmaceuticals, San Diego, California) is an injectable synthetic analog of human amylin. Amylin is a naturally occurring neuroendocrine hormone cosecreted by pancreatic β cells with insulin. The insulin/amylin ratio secreted by the normal

pancreas is approximately 50:1, although a 20:1 ratio is seen in the peripheral circulation attributable to hepatic metabolism of insulin.[1] The β-cell malfunction causing absolute and relative insulin deficiencies seen in type 1 and type 2 diabetes also results in decreased endogenous amylin secretion. Unlike insulin, which lowers blood glucose by increasing glucose disposal, amylin works by decreasing postprandial glucose appearance in the circulation by lowering inappropriate postmeal glucagon secretion (glucagon stimulates the liver to make glucose from glycogen stores), slowing gastric emptying, increasing satiety, and reducing food intake.[2-4] Pramlintide is given just prior to meals and is approved as an adjunct treatment in patients with type 1 or type 2 diabetes 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.[5]

Benefits, Patient Selection, and Dosing

The benefits of pramlintide include reduction of postprandial glucose and A1C levels, potential reduction of total daily insulin dose, and possible weight loss. Pramlintide typically reduces 2-hour postprandial glucose between 43 and 90 mg/dL and has a minimal effect on fasting glucose.[6] Postprandial hyperglycemia has been reported to increase the risk of atherosclerotic events independent of its contribution to A1C.[6] Postprandial glycemic excursions are not only an important component of overall glycemic exposure: the relative contribution of postprandial glucose to overall glucose control is proportionally greater than that of fasting glucose as one approaches the American Diabetes Association target A1C of less than 7%.[7] Studies indicate that pramlintide reduces A1C between 0.2% and 0.4% in patients with type 1 diabetes and 0.4% and 0.6% in patients with type 2 diabetes (from a baseline A1C of 8%-9%).[4] Improved diabetes control has been shown to reduce the risk of diabetes-related complications.[8-11] The 0.5- to 1-kg weight loss observed with pramlintide therapy may be beneficial compared with the increase in weight that is commonly seen with the use of insulin, sulfonylureas, and thiazolidinediones.

The major limitations to pramlintide therapy include hypoglycemia (when used with insulin), nausea, and its subcutaneous route of administration. Hypoglycemia generally occurs within 3 hours after injection. The rate of hypoglycemia in pramlintide-treated patients in clinical trials was 2- to 4-fold greater than the placebo group's rate during the first 4 weeks of therapy.[12,13] The risk of hypoglycemia, especially in patients with type 1 diabetes, resulted in a boxed warning for hypoglycemia being placed in the Symlin package insert when the drug was approved in 2005. However, these early clinical trials used fixed doses of both pramlintide and insulin.[12-15] Subsequent to these clinical trials, a study designed to reduce mealtime insulin doses by 30% to 50% with the initiation of pramlintide found a significant decrease in severe hypoglycemia.[16] The manufacturer recommends reducing the dose of premeal insulin (rapid acting, short acting, or fixed-mixed insulin) by 50% when starting pramlintide. No dose adjustment of baseline sulfonylurea or metformin therapy is recommended. Patients taking basal insulin may need to adjust their subsequent basal insulin doses depending on their fasting blood glucose results.[17] As a result of the need for titration of both insulin and pramlintide, therapy should only be considered for patients who are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin.

Appropriate patient selection, careful patient instruction, and insulin dose adjustments help reduce the risk of hypoglycemia. Pramlintide is not an ideal medication choice for patients who struggle with the demands of self-management of their diabetes. This is a medication for patients who need modest glycemic (primarily postprandial) improvement and have the knowledge, skills, and motivation to manage their diabetes.

Mealtime insulin doses should be reduced by 50% at pramlintide initiation and adjusted as the pramlintide dose is increased to minimize the risk of hypoglycemia. For patients with type 1 diabetes, pramlintide is initiated at 15 μg and is increased based on tolerability to 30 or 60 μg with meals, up to 4 times daily. If the 30-μg dose is not tolerated in patients with type 1 or type 2 diabetes, discontinuation of the drug should be considered. In patients with type 2 diabetes, pramlintide is initiated at 60 μg and is increased based on tolerability to 120 μg 2 to 3 times daily with meals. Close monitoring of blood glucose levels is imperative when pramlintide therapy is started in order to avoid insulin-induced severe hypoglycemia. Close monitoring is especially important when operating a motor vehicle or heavy machinery. Patients should always have treatment for hypoglycemia (glucose

tablets, juice, candy, or glucagon) available in case of hypoglycemia. Blood glucose levels should be checked prior to and after each meal and at bedtime with the initiation of pramlintide. Once target pramlintide doses are reached, pramlintide doses should remain stable, with only insulin doses being adjusted according to blood glucose results. Finally, supplemental insulin correction doses should be reevaluated because the reduced requirements of insulin with the use of pramlintide can increase the risk of hypoglycemia if previous insulin correction doses are used. If pramlintide is discontinued because of the need for surgery or other illness and is later reinitiated, the initial dose and dose titration schedule of pramlintide (with 50% reduction in bolus insulin) should be used.

Nausea was the most frequently reported side effect and the most common reason for subject withdrawal in clinical trials, although nausea typically dissipated after a month of therapy. To reduce nausea, pramlintide should be injected with the first bite of a meal, and low doses of medication are recommended at drug initiation (eg, 15 µg for type 1 patients, 60 µg for type 2 patients). Starting at low doses as well as waiting 3 or more days without nausea before increasing the dose or dosing frequency can also reduce nausea. Initiating pramlintide therapy once daily with the largest meal before increasing to twice- and thrice-daily dosing can increase drug tolerability. Pramlintide is commonly started prior to dinner at the lowest recommended dose. The pramlintide dose is increased over several days along with adjustment of predinner insulin doses evaluated based on postprandial blood glucose readings. This approach continues with a second daily dose given with the next largest meal of the day (typically lunch) and then is repeated for the smallest meal of the day (typically breakfast). For the patient who cannot tolerate 3 doses, continue with twice-daily therapy if the 2 postmeal blood glucose levels have responded favorably.

Practical Considerations

Once the focused period of titration of both pramlintide and mealtime insulin doses has occurred, patients may occasionally miss a dose of pramlintide. When this occurs, the patient should be counseled to inject premeal insulin (either via injection or pump bolus) with the predetermined carbohydrate ratio and correction factor used when taking pramlintide. The 2-hour postmeal blood glucose reading after a missed dose of pramlintide is imperative because this value will most likely be elevated. The patient will need to give a correction insulin dose using the correction factor calculated when taking pramlintide. Another (arguably more favorable) strategy to avoid the postprandial hyperglycemia associated with a missed dose of pramlintide is to prospectively provide the patient with 2 different insulin to carbohydrate ratios, 1 when using pramlintide and 1 if the pramlintide dose is missed (this will likely be close to the patient's prepramlintide insulin to carbohydrate ratio). This strategy easily fits the needs of patients taking insulin injections. If using an insulin pump with insulin to carbohydrate ratios programmed based on pramlintide, patients will need to be instructed on how to adjust their pump bolus to account for the lack of premeal pramlintide.

To match the delayed gastric emptying caused by pramlintide with the peak action of meal time insulin, some patients have benefitted from dosing insulin after eating. Patients who use an insulin pump may benefit from using the extended bolus feature. Postprandial blood glucose monitoring or continuous glucose monitoring results will help the patient determine the best time and method for dosing meal time insulin.

Pramlintide should be administered by subcutaneous injection into the thigh or abdomen before each major meal (defined as >250 kcal or 30 g of carbohydrate).[5] Administration into the arm is not recommended because of variability in drug absorption.[5] Injection sites should be rotated and should be a minimum of 2 inches from the insulin injection site.[5] To reduce potential injection site reactions, patients should allow the pramlintide pen stored in the refrigerator to come to room temperature prior to injection. Pramlintide is a clear fluid so it should not be used if the liquid appears cloudy. If a meal is skipped, the pramlintide dose should be omitted. A new 31-gauge, 5/16-inch pen needle should be used for each injection using the pen injector.

Pramlintide is available as the SymlinPen 60 pen injector (1000 µg/mL, 1.5 mL) and the SymlinPen 120 pen injector (1000 µg/mL, 2.7 mL). Given the potential for dosing errors, the US Food and Drug Administration required the manufacturer of Symlin (pramlintide) to remove pramlintide vials from the market as of January 2011. Table 1 provides dosing guidelines for patients who are still using vials. Unopened pramlintide should be stored in the refrigerator (36-46°F, 2-8°C) and protected from light until ready to use. Freezing will destroy

Table 1

Pramlintide Vial Dosing

Dose, µg	Unit Equivalents, U	Volume, mL
15	2.5	0.025
30	5	0.05
45	7.5	0.075
60	10	0.1
120	20	0.2

Given the potential for dosing errors, the US Food and Drug Adminstration required the manufacturer of Symlin (pramlintide) to remove the pramlintide vial from the market as of January 2011. To minimize potential dosing errors, use of the pramlintide pen is recommended. For patients who are still using the vial, a 0.3-mL U-100 insulin syringe is recommended for dosing accuracy. A new needle and syringe should be used for each injection, and the dose should be expressed in micrograms. Pramlintide should never be mixed in the same syringe with insulin.[21] The 5-mL vial was available as 600 µg/mL. When converting to delivery of pramlintide via pen injector, patients will require instruction concerning use of the SymlinPen.

the medication. A pen injector once opened can be refrigerated or kept at room temperature (up to 86°F) for 30 days. Pen injectors in use after 30 days should be discarded (even if medication remains). The SymlinPen 60 pen injector and the SymlinPen 120 pen injector cost about $310 for a box of 2 pens.[18] Monthly costs will vary depending on the dose. For example, a type 1 patient receiving 60 µg 3 times per day will require 3.6 of the 60 pen injectors (2 boxes) per month, and a type 2 patient receiving 120 µg 3 times per day will require 4 of the 120 pen injectors (2 boxes) per month. Caution should be exercised to differentiate pramlintide pens from insulin pens.

Because pramlintide slows gastric emptying, it is not recommended for use in patients with a confirmed diagnosis of gastroparesis. Pramlintide has been studied in moderate to severe renal insufficiency and requires no dosage adjustments in patients with a creatinine clearance greater than 20 mL/min. No studies have been conducted using pramlintide in patients with end-stage renal disease. In addition, a patient history of frequent hypoglycemia or hypoglycemic unawareness is a relative contraindication to pramlintide because it will increase the risk of low blood glucose levels when used in combination with insulin or sulfonylurea therapies. Therapy with pramlintide is not recommended in patients who do not adhere to their current insulin therapy or monitor blood glucose levels as prescribed.[4] Pramlintide is not an ideal medication choice in patients with significantly elevated A1C (>9%), in patients less than 18 years of age, and in patients receiving concomitant therapy with medications that stimulate gastrointestinal motility (eg, erythromycin, metoclopramide, cisapride).

Minimizing Patient Frustration, Maximizing Tolerability and Success

Prior to initiation of pramlintide, it is especially important to discuss with patients that hyperglycemia is common in the initial phase of therapy because of the initial 50% reduction in mealtime insulin dosages. The drastic reduction in mealtime insulin doses is required to minimize the risk of hypoglycemia. Although this can be frustrating to the patient, starting with a low pramlintide dose helps to minimize the incidence of nausea and vomiting, and the 50% reduction in mealtime insulin dose decreases the risk of hypoglycemia. Using these strategies increases the likelihood of patient tolerability and safety.

The diabetes educator plays a crucial role in teaching patients how to interpret their blood glucose readings. With the initiation of pramlintide therapy, postprandial glucose trends need to be evaluated in terms of the pramlintide dose, insulin dose, and composition of the meal. The diabetes care team should provide the patient with specific guidelines for using trending data for dose titration and also provide close follow-up. Patients will be learning many new skills and will benefit from the services of a diabetes educator.

Pramlintide is not indicated for use in patients with type 2 diabetes treated with basal insulin only. This off-label, basal insulin–bolus pramlintide approach is intended to improve glycemic control while minimizing the weight gain associated with insulin therapy. In a study of the addition of pramlintide to insulin glargine in patients with type 2 diabetes, Riddle et al[17] reported improved A1C (0.7%) and weight reduction (mean 1.6 kg) compared with placebo. There was no documented increase in hypoglycemia during this 16-week study.

Providers and educators should be aware of the off-label use of pramlintide as a continuous infusion. In a 16-week pilot study of 11 patients with type 1 diabetes who were using insulin pumps filled with pramlintide, a continuous subcutaneous pramlintide infusion improved A1C, lowered mean fasting glucose levels from 182 mg/dL to 136 mg/dL, reduced insulin bolus doses by 20%, and reduced weight by 0.5 kg.[19] The study used a basal

Table 2

Top 10 Patient Counseling Points for Symlin

When used with premeal insulin, Symlin has been associated with an increased risk of severe hypoglycemia.
The premeal insulin dose should be decreased by 50% when Symlin is initiated and adjusted as needed thereafter to decrease the risk of low blood sugars.
Patients should always keep treatment for hypoglycemia and/or glucagon on hand. Patients are also encouraged to wear a medical alert bracelet at all times.
Symlin is injected into the thigh or abdomen with the first bite of food with any meal that is >250 kcal or 30 g of carbohydrates. Symlin should be injected a minimum of 2 inches away from the premeal insulin injection site. Sites should be rotated with each injection.
Close monitoring of blood glucose is very important. Blood glucose should be checked before operating a motor vehicle or heavy machinery, prior to and/or after each meal, and at bedtime.
Nausea is the most common side effect associated with Symlin use. This generally resolves within a month. Initiating therapy at a low dose and beginning with once-daily dosing at the largest meal with slow titration will increase tolerability.
Symlin doses should be increased to the targeted dose prior to adding a second or third daily dose. Repeat until 3 target daily doses are reached.
Once the desired dose of Symlin is achieved (and tolerated), insulin doses should be adjusted toward target blood glucose levels while the Symlin dose is kept the same.
Unopened Symlin pens should be stored in the refrigerator. Allow the medication to come to room temperature prior to injection. Once open (and at room temperature), Symlin pens are stable for 30 days. The medication should appear clear. If it is cloudy or colored or has any precipitant, it should not be used. Do not allow Symlin to freeze.
Symlin should not be used in patients with a history of recurrent and severe hypoglycemia or in patients with asymptomatic hypoglycemia. Symlin should not be used in patients with gastroparesis or those who are pregnant, are planning to become pregnant, or are breastfeeding.

pramlintide dose of 9 µg/h with bolus doses initiated at 15 µg and titrated to 60 µg per meal.

Concomitant administration of oral agents with pramlintide can reduce the rate of absorption of the oral agents. Pramlintide slows the absorption of acetaminophen but does not affect the total amount absorbed.[20] If a rapid onset of effect is required, oral agents should be administered 1 hour before or 2 hours after pramlintide injection. The manufacturer recommends separating the administration of analgesics by 1 hour before or 2 hours after administration of pramlintide to prevent a delay in the analgesic effect.[4] Alcohol can increase the risk of hypoglycemia. Pramlintide can increase the effects of anticholinergic agents (eg, benztropine, amantadine, scopolamine).

Pramlintide is not approved for use during pregnancy or in nursing mothers. It is a pregnancy category C drug because of adverse effects observed in animal studies. Pramlintide has not been studied in pregnant or lactating women. Although in vitro data have shown that pramlintide is unlikely to cross the placenta, it is not known whether pramlintide is harmful to a fetus or whether it passes into breast milk. Women should inform their providers if they plan to become pregnant or breast-feed.

Table 2 provides a concise list of counseling points for health care providers. The diabetes team provides individualized feedback and serves as advocates for patients initiating pramlintide therapy. To further assist patients, Amylin Pharmaceuticals provides a 24-hour customer service (800-349-8919) and has the Symlin Support Program, which is staffed by nurses and nurse Certified Diabetes Educators and is available to patients via the Web (www.SYMLINsupport.com) and by telephone (1-888-SYMLIN1, or 1-888-796-5461).

Summary

Pramlintide treats diabetes with a novel mechanism of action, offering the potential for improved postprandial

control and weight loss for patients with type 1 or type 2 diabetes. Providers and diabetes educators should be familiar with the utility of the medication as well as its potential limitations in order to fully educate patients and maximize treatment options for patients with diabetes.

Note

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References

1. Kruger DF, Gatcomb PM, Owen SK. Clinical applications of amylin and amylin deficiency. *Diabetes Educ*. 1999;25:389-397.
2. Fineman MS, Koda JE, Shen LZ, et al. The human amylin analogue, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. *Metabolism*. 2002;51:636-641.
3. Vella A, Lee JS, Camilleri M, et al. Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and 2 diabetes mellitus. *Neurogastroenterol Motil*. 2002;14:123-131.
4. Chapman I, Parker B, Doran S, et al. Effect of pramlintide on satiety and food intake in obese subjects and subjects with type 2 diabetes. *Diabetologia*. 2005;48:838-848.
5. Symlin® [package insert]. San Diego, CA: Amylin Pharmaceuticals; 2008.
6. The DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999;354:617-621.
7. Monnier L, Lapinski H, Colette 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). *Diabetes Care*. 2003;26:881-885.
8. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Eng J Med*. 1993;329:977-986.
9. UK Prospective Diabetes Study (UKPDS) group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837-853.
10. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117.
11. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.
12. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated patients with type 2 diabetes. *Diabetes Technol Ther*. 2002;4:51-61.
13. 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;26:784-790.
14. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care*. 2002;25:724-730.
15. 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. *Diabet Med*. 2004;21:1204-1212.
16. Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in Type 1 diabetes. *Diabetes Care*. 2006; 29:21-95.
17. Riddle M, Frias J, Zhang B, et al. Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes Care*. 2007;30:2794-2799.
18. Drugstore.com the uncommon drugstore. 2010. http://www.drugstore.com/pharmacy/prices/drugprice.asp?ndc=66780012102&trx=1Z5006. Accessed February 18, 2010.
19. Huffman DM, McLean GW, Seagrove MA. Continuous subcutaneous pramlintide infusion therapy in patients with type 1 diabetes: observations from a pilot study. *Endocr Pract*. 2009;15: 689-695.
20. Kellmeyer TA, Kesty NC, Wang Y, et al. Pharmacokinetics of an oral drug (acetaminophen) administered at various times relative to subcutaneous injection of pramlintide in subjects with type 2 diabetes. *J Clin Pharmacol*. 2007;47:798-805.
21. Weyer C, Fineman M, Strobel S, et al. Properties of pramlintide and insulin upon mixing. *Am J Health Syst Pharm*. 2005;62: 816-822.