COMMENTARY

Rediscovery of the Second β-Cell Hormone: Co-replacement With Pramlintide and Insulin in Type 1 Diabetes

Matthew C. Riddle

Diabetes Care 2020;43:518–521 | https://doi.org/10.2337/dci19-0077

Insulin is always deficient relative to need in diabetes. Injected insulin is essential to replace the complete lack of insulin in type 1 diabetes and to supplement endogenous insulin for many people with type 2 diabetes. Unfortunately, despite advances in insulin formulation and delivery and the effects of other glucose-lowering therapies instead of or in combination with insulin, the goals of therapy are seldom completely met. People using insulin (especially prandial insulin) are at risk for hypoglycemia and weight gain, and their postprandial glucose levels are rarely well controlled. Surprisingly, an obvious contributor to this dilemma has received little attention—a concurrent deficiency of the hormone amylin in all people with diabetes.

Amylin was isolated and characterized three decades ago (1,2), about 70 years after insulin therapy became available, and "co-replacement therapy" with insulin and amylin was soon proposed for type 1 diabetes (3). Delay in characterization of amylin was partly due to its tendency to self-aggregate and cling to glass or plastic surfaces. In some species, notably cats and humans, amylin aggregates as "amyloid" in the endocrine pancreas and may contribute to injury of β-cells (4). Studies have been further hampered by difficulties in assaying amylin levels in blood, where significant proportions are modified and likely inactive (5). Even so, much has been learned about amylin's distribution, regulation, and physiologic functions in animal and human studies (6). It is a 37–amino acid peptide that is produced in the pancreatic β-cell and secreted in parallel with insulin, and thus it is lacking in type 1 diabetes (6,7). Although present in other parts of the body, amylin is released into the blood only by β-cells. The actions of secreted amylin are mediated through parts of the brain that are outside the blood-brain barrier, and effects elsewhere depend on neural signals relayed by the central nervous system (6). Three effects are highly relevant to diabetes: *1*) modulation of gastric emptying, which can be abnormally rapid in diabetes; *2*) suppression of glucagon, which is secreted excessively in diabetes, especially after meals; and *3*) development of satiety soon after starting a meal. Together with insulin, these effects limit hyperglycemia after meals and prevent excessive calorie intake.

Amylin itself is not suited for therapeutic use due to instability in solution. Pramlintide, an analog of amylin, has better properties. It is stable in solution and cleared from circulation slightly less rapidly than amylin (8). Subcutaneous injection leads to peak blood levels by 30 min with a return to baseline in 2 to 3 h (9). Pramlintide binds to and activates amylin receptors very much like amylin and has similar effects on gastric emptying, glucagon secretion, and satiety (10–13). Subcutaneous doses of 30 μg or higher markedly blunt postprandial increases of glucose in type 1 diabetes (9). Fortunately, responses of glucagon to hypoglycemia in type 1 diabetes are not altered by pramlintide (9).

Development of pramlintide as a commercial product (Symlin) proved difficult. A 52-week randomized trial in type 1 diabetes using 60-μg mealtime doses showed a placebo-adjusted reduction of HbA_{1c} of just 0.3%, and only 63% of participants completed the study (14). Approved only for addition to basal-bolus therapy, Symlin requires a separate injection with each meal in addition to insulin injections. Postprandial hypoglycemia can occur unless prandial insulin is correctly adjusted. Initial or intermittent dosing causes nausea for some people, although this problem subsides with ongoing use. Partly because of these difficulties, Symlin has not been widely used from the time of its approval in 2005 to the present.

However, after expiration of the patent for Symlin, interest in pramlintide for type 1 diabetes has revived. Three proof-of-concept studies using pramlintide to enhance the effects of continuous subcutaneous insulin infusion (CSII) have been reported in *Diabetes Care*. All were single-day studies of small groups of people with type 1 diabetes, but they used somewhat different protocols (Table 1).

Division of Endocrinology, Diabetes & Clinical Nutrition, Department of Medicine, Oregon Health & Science University, Portland, OR

Corresponding author: Matthew C. Riddle, riddlem@ohsu.edu

See accompanying article, p. 597.

Table 1—Design features, populations enrolled, and selected outcomes of three proof-of-concept studies of coadministration of insulin and pramlintide for type 1 diabetes. Mean values are shown.

	Study		
Characteristic	Sherr et al. (15)	Riddle et al. (16)	Haidar et al. (17)
Number of participants	10	26	27
Age (years)	20	41	35
Duration T1D (years)	9	24	23
Baseline HbA_{1c} (%)	7.2	8.1	7.8
Duration of intervention	24 h	24 h	24 h
Comparison	Rapid insulin CSII vs. rapid insulin CSII + pramlintide mealtime injections	Regular insulin CSII + placebo CSI vs. regular insulin CSII + pramlintide CSI	Rapid insulin CSII vs. rapid insulin CSII + pramlintide CSI
Pram/insulin ratio (μg/unit)	—	9	6
Dosing algorithm	Automated closed-loop basal without boluses	Fixed basal rate and fixed bolus doses selected by investigators	Adaptive closed-loop basal and bolus administered by investigators
Bolus pram dose (μg)			
Breakfast	60	53	Mean all meals 34
Lunch	60	45	Mean all meals 34
Dinner	60	68	Mean all meals 34
Total daily insulin dose (units)			
CSII alone	—	38.8	38.4
CSII + pram	—	35.2	37.9
Mean CGM glucose			
CSII alone (mg/dL)	166	175	144
CSII alone (mmol/L)	9.2	9.7	8.0
CSII + pram (mg/dL)	160	153	133
CSII + pram (mmol/L)	8.9	8.5	7.4
Difference (mg/dL)	−6	−22	−11
Difference (mmol/L)	−0.3	−1.2	−0.6
P for difference	$P = 0.08$	$P = 0.012$	$P = 0.001$
TIR (70–180 mg/dL), 24 h			
CSII alone	—	50.2	74
CSII + pram	—	61.5	84
P for difference	—	$P = 0.046$	$P = 0.001$
TIR (70–180 mg/dL), 0800–2300 h			
CSII alone	59.7	—	63
CSII + pram	71.0	—	78
P for difference	$P = 0.004$	—	$P = 0.0004$

CSI, continuous subcutaneous infusion; pram, pramlintide; T1D, type 1 diabetes.

One of these studies (15) enrolled 10 participants with good glycemic control on open-loop CSII using rapid-acting insulin who were admitted for two 24-h inpatient studies, one with and one without subcutaneous injection of 60-μg doses of pramlintide prior to each of three meals. During the inpatient studies, insulin was delivered by a fully automated closed-loop system without mealtime boluses. Meals were self-selected but the same for each regimen. Pramlintide delayed postprandial increments of glucose and reduced peak increments by 39% ($P = 0.002$). The mean daytime (0800–2300 h) time in range (TIR) (70–180 mg/dL [3.9–10.0 mmol/L]) by continuous glucose monitoring (CGM) was 59.7% without and 71.1% with pramlintide ($P = 0.004$). The total insulin dose administered was lower with pramlintide, 28.2 versus 32.6 units ($P = 0.047$).

In another study (16), 26 participants had glycemic control stabilized with CSII using rapid-acting insulin prior to two random-order 24-h inpatient protocols. Participants but not investigators were masked to treatment assignment. CSII with human regular insulin plus placebo was compared with CSII with regular insulin plus continuous infusion of pramlintide at a fixed ratio of 9 μg per unit of insulin. Separate open-loop infusion systems were used. Isocaloric meals were similar between participants and regimens. Basal and prandial insulin doses and corresponding quantities of pramlintide or placebo for each participant were selected by the investigators based on experience during the run-in and were the same with each regimen. Basal rates were constant over 24 h. Mean glucose by CGM was 1.2 mmol/L (22 mg/dL) lower with pramlintide ($P = 0.012$) because of a

marked reduction of postprandial increments. Pramlintide increased the 24-h TIR from 50.2% to 61.5% ($P = 0.046$). The coefficient of variation of glucose was 0.35 with insulin alone and 0.31 with the combination regimen ($P = 0.062$).

A report by Haidar et al. (17) in this issue of *Diabetes Care* adds significantly to this prior experience. Their study compared CSII with insulin lispro alone with continuous delivery of pramlintide together with lispro or regular human insulin in a fixed ratio of 6 μg per unit of insulin. Separate closed-loop infusion systems were used. Four participant-selected meals were provided. A run-in period established optimal basal rates, carbohydrate-to-insulin ratios, and insulin sensitivity factors, which were used in an adaptive algorithm guiding basal and bolus dosing during two 24-h inpatient studies. Twenty-seven participants had complete data for the main end point, a comparison of TIR with closed-loop lispro alone versus closed-loop lispro and pramlintide together. The fixed-ratio combination regimen increased 24-h TIR from 74% to 84% ($P = 0.001$), reduced mean glucose by 0.6 mmol/L (9 mg/dL) ($P = 0.005$), and reduced the glucose coefficient of variation from 0.303 to 0.268 ($P = 0.035$). Between-treatment differences were clearest during the daytime (0800–2300 h), when postprandial glycemic increments were markedly blunted and TIR increased from 63% to 78% ($P = 0.0004$). A similar comparison of closed-loop rapid-acting insulin alone versus closed-loop regular human insulin coadministered with pramlintide showed no advantage of the combined regimen. However, conclusions regarding regular versus rapid-acting insulin in this setting were limited by differences in dosing tactics. An overly quick effect of rapid-acting insulin was avoided by a modified square-wave delivery in the first 20 min after meals, while the slower onset of regular insulin was anticipated by beginning a different square-wave pattern 20 min before meals. Pramlintide infusions were to match the delivery of insulin. However, parameters guiding the closed-loop system that were derived from experience with rapid-acting insulin might be less appropriate for regular insulin under these conditions.

These studies of co-replacement therapy including CSII show quantitatively impressive blunting of postprandial increments and overall variability of glucose and verify tolerability. They also provide important new insights. Two studies (16,17) showed no effect of infusion of pramlintide during the night, directing attention instead to the prandial effects. In the study by Haidar et al. these effects were attained with relatively small boluses of pramlintide, confirming other evidence (18) suggesting that boluses of 6 μg (or less) per unit of insulin may be enough to control postprandial hyperglycemia when given with properly regulated insulin.

Nonetheless, important questions remain. Does it matter whether regular human insulin or a rapid-acting analog is used together with pramlintide? Similar flattening of daytime glucose profiles was attained with regular insulin in one study (16) and in another with rapid-acting insulin (17). Perhaps either can be effective if the dosing algorithm is adjusted to the pharmacodynamics of the insulin used. Will continuous pramlintide infusion limit side effects by occupying receptors day and night, improving long-term tolerability? The low incidence of nausea following a run-in on pramlintide in the study by Haidar et al. supports this view. Can the flat glucose profiles seen in these short-term studies safely be sustained in longer ambulatory studies together with reduction of basal levels? Specifically, can ongoing adjustment of 24-h delivery of fixed-ratio insulin and pramlintide for 12 to 16 weeks attain HbA_{1c} levels near or below 7% without problematic hypoglycemia or nausea? What changes of closed-loop algorithms developed for use with insulin alone may be needed for the best results with co-replacement? Quite likely, these will include a smaller bolus of both insulin and pramlintide before each meal, followed by enhanced glucose-dependent delivery of both agents during a 4-h absorptive period and retention of the modest adjustments currently used under postabsorptive (basal) conditions.

Longer-term studies to answer these questions will depend on technical advances. Concurrent use of two infusion systems is not practical, but there are other options. A two-channel system might deliver an amylin analog and insulin from separate reservoirs, or a stable coformulation of the two molecules might be developed for infusion by existing devices. Both options seem feasible, and clinical application of the principle proven in the present studies depends on them. The good news for now is that we are rediscovering that diabetes is a two-hormone deficiency disorder and beginning to test the potential of co-replacement by continuous infusion systems to overcome the limitations of replacing insulin alone.

Duality of Interest. M.C.R. reports receiving research grant support through Oregon Health & Science University from AstraZeneca, Eli Lilly, and Novo Nordisk and honoraria for consulting from Adocia, AstraZeneca, Dance, Eli Lilly, GlaxoSmithKline, Novo Nordisk, Sanofi, and Theracos. These dualities of interest have been reviewed and managed by Oregon Health & Science University. The present work was supported in part by the Rose Hastings and Russell Standley Memorial Trusts.

References

1. Westermark P, Wernstedt C, O'Brien TD, Hayden DW, Johnson KH. Islet amyloid in type 2 human diabetes mellitus and adult diabetic cats contains a novel putative polypeptide hormone. Am J Pathol 1987;127:414–417
2. Cooper GJ, Willis AC, Clark A, Turner RC, Sim RB, Reid KBM. Purification and characterization of a peptide from amyloid-rich pancreases of type 2 diabetic patients. Proc Natl Acad Sci U S A 1987;84:8628–8632
3. Cooper GJS. Amylin and insulin co-replacement therapy for insulin-dependent (type I) diabetes mellitus. Med Hypotheses 1991;36:284–288
4. Jurgens CA, Toukatly MN, Fligner CL, et al. β-Cell loss and β-cell apoptosis in human type 2 diabetes are related to islet amyloid deposition. Am J Pathol 2011;178:2632–2640
5. Percy AJ, Trainor DA, Rittenhouse J, Phelps J, Koda JE. Development of sensitive immunoassays to detect amylin and amylin-like peptides in unextracted plasma. Clin Chem 1996;42:576–585
6. Young A. *Amylin: Physiology and Pharmacology*. Vol. 52: Advances in Pharmacology. Cambridge, MA, Academic Press, 2005
7. Koda JE, Fineman M, Rink TJ, Dailey GE, Muchmore DB, Linarelli LG. Amylin concentrations and glucose control. Lancet 1992;339:1179–1180
8. Colburn WA, Gottlieb AB, Koda J, Kolterman OG. Pharmacokinetics and pharmacodynamics of AC137 (25,28,29 tripro-amylin, human) after intravenous bolus and infusion doses in patients with insulin-dependent diabetes. J Clin Pharmacol 1996;36:13–24
9. Kolterman OG, Schwartz S, Corder C, et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard liquid meal in patients with IDDM. Diabetologia 1996;39:492–499
10. Fineman MS, Koda JE, Shen LZ, et al. The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. Metabolism 2002;51:636–641
11. Hinshaw L, Schiavon M, Dadlani V, et al. Effect of pramlintide on postprandial glucose fluxes in type 1 diabetes. J Clin Endocrinol Metab 2016;101:1954–1962

12. Galderisi A, Sherr J, VanName M, et al. Pramlintide but not liraglutide suppresses meal-stimulated glucagon responses in type 1 diabetes. J Clin Endocrinol Metab 2018;103:1088–1094
13. 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
14. 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
15. Sherr JL, Patel NS, Michaud CI, et al. Mitigating meal-related glycemic excursions in an insulin-sparing manner during closed-loop insulin delivery: the beneficial effects of adjunctive pramlintide and liraglutide. Diabetes Care 2016; 39:1127–1134
16. Riddle MC, Nahra R, Han J, et al. Control of postprandial hyperglycemia in type 1 diabetes by 24-hour fixed-dose coadminstration of pramlintide and regular human insulin: a randomized, two-way crossover study. Diabetes Care 2018;41:2346–2352
17. Haider A, Tsoukas MA, Bernier-Twardy S, et al. A novel dual-hormone insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomized controlled crossover trial. Diabetes Care 2020; 43:597–606
18. Riddle MC, Yuen KCJ, de Bruin TW, et al. Fixed ratio dosing of pramlintide with regular insulin before a standard meal in patients with type 1 diabetes. Diab Obes Metab 2015;17:904–907