Pramlintide Use in Type 1 Diabetes Resulting in Less Hypoglycemia

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Presentation

S.D. is a 49-year-old white man who has had type 1 diabetes for 43 years. He has been on an intensive insulin regimen since 1982, when he began attending the diabetes clinic. At that time, his program consisted of ultralente twice daily and regular insulin before each meal. His total daily insulin dose was 45 units per day. He was testing his blood glucose four to six times daily with a home blood glucose monitor.

Presently, S.D. has background diabetic retinopathy. He has no other known diabetes complications. He has been on a statin medication since 2002 for hyperlipidemia. His total cholesterol was 219 mg/dl, LDL cholesterol was 139 mg/dl, and HDL cholesterol was 69 mg/dl when medication was initiated. For a period of time, he was treated with an antidepressant, but he has been off this medication since a job change. He no longer feels an antidepressant is needed.

Eight years ago, S.D.'s BMI was 28 kg/m^2; his weight was 198 lb, and his height was 70.5 inches. Two years ago, his weight was 242 lb, and his BMI was 34 kg/m^2. With the intensification of his insulin regimen and lowering of his blood glucose and hemoglobin A_{1c} (A1C), he has progressively gained weight.

In 1996, S.D.'s regimen changed from ultralente and regular insulin to ultralente and lispro. This regimen change decreased his hypoglycemia, especially nocturnal hypoglycemia. His A1C ranged from 5.6 to 8.0% (normal range 2.9–7.1) during this 10-year period. He remained on this regimen until 2001, when he began subcutaneous insulin pump therapy to help prevent frequent hypoglycemia and improve his hypoglycemia awareness. He weighed 228 lb (BMI 32.2 kg/m^2) when he began insulin pump therapy.

His A1C range while on the insulin pump was 6.9–7.8% (normal range 3.4–6.2). His total insulin dose on the insulin pump before discontinuing the pump was 38 units per day. S.D. discontinued insulin pump therapy because of his frustration with weight gain and increasing hypoglycemia unawareness. In 2003, he had an automobile accident that was attributed to hypoglycemia. During the past 20 years, S.D. has experienced one to two episodes each year of hypoglycemia requiring assistance.

In 2003, he began glargine with three injections of lispro before meals. His total dose was 39 units per day. S.D. reported less hypoglycemia with the switch to glargine but still experienced widely fluctuating blood glucose levels. By decreasing his insulin dose and taking a proactive approach to more frequent blood glucose monitoring, S.D. was able to improve his hypoglycemia awareness.

S.D. has been using a calorie point meal planning system since 1982. He eats ~ 2,200 calories per day divided into three meals. He snacks only if his activity warrants extra calories. He doses his insulin based on carbohydrates and calories ingested. He also uses the 1,500 rule for correcting hyperglycemia, which is ~ 1 unit to decrease blood glucose by 40 mg/dl.

S.D. is married and has two children. As a school janitor, his activity is quite variable. His hours also can be variable, depending on evening activities at school. He usually arrives at school by 5:00 A.M. to begin work.

Questions

1. Considering S.D.'s history of hypoglycemia, would he be a candidate for pramlintide?
2. How would one titrate the insulin and pramlintide doses in this patient with type 1 diabetes?
3. What would be the recommended clinical follow-up for this patient?
4. How often should this patient check his blood glucose?

Discussion

The Diabetes Control and Complications Trial demonstrated that intensive insulin therapy reduces the appearance and progression of microvascular complications in type 1 diabetes.[1] During this study, it was also noted that the patients who received intensive insulin therapy were at increased risk for hypoglycemia and weight gain.[2] Recently, a new class of medication has been shown to reduce postprandial glucose fluctuation with the potential for reduced hypoglycemia and weight loss.[3]

The hormone amylin works with insulin to suppress glucagon secretion. It also regulates gastric emptying, which influences the rate of glucose appearance in the circulation. This gastric slowing is actually normalization because it has been shown that patients with diabetes have accelerated gastric emptying. Amylin also induces earlier satiety and thus can decrease food intake. All of these actions lead to a lowering of the postprandial blood glucose.[4] Amylin acts as an antihyperglycemic rather than a hypoglycemic.[3] Pramlintide is an analog of the naturally occurring pancreatic hormone amylin. Pramlintide does not cause hypoglycemia, but

when used with insulin, it can cause insulin-induced hypoglycemia.

Nausea and hypoglycemia are the most common side effects of pramlintide therapy.[3] The nausea has been described as mild to moderate in studies and has typically dissipated after 4–8 weeks. Hypoglycemia has been similar between study groups.[2,3]

Considering S.D.'s widely fluctuating blood glucose levels, frequent hypoglycemia, persistent postprandial hyperglycemia, and weight gain, despite intensive insulin regimens and diabetes self-management skills, he was asked if he would like to participate in a clinical trial using pramlintide. He agreed and consented to participate in the trial, which began > 2 years ago.

S.D. was considered an excellent candidate because he was motivated to improve his blood glucose control, test his blood glucose levels frequently, and maintain frequent contact with the clinic as we assisted in adjusting his insulin doses and titrated his pramlintide doses. He also had widely fluctuating postprandial blood glucose levels.

He was having frequent hypoglycemia with symptoms occurring in the low 50-mg/dl range. We would have preferred that he have symptoms in the 60–70 mg/dl range. He had not required assistance in treating an episode of hypoglycemia in nearly a year. He had no history of delayed gastric emptying.

S.D. was scheduled for education regarding initiating pramlintide therapy. He was instructed that pramlintide is administered by subcutaneous injection in the thigh or abdomen using a 30-unit insulin syringe. Pramlintide cannot be mixed with insulin; separate syringes should be used for insulin and pramlintide. Pramlintide is administered with each meal or snack that consists of at least 250 calories or 30 g of carbohydrate. It can be administered up to four times daily.

Individuals with type 1 diabetes begin dosing with 15 μg (2.5 units) and titrate based on whether they experience nausea. If there is no nausea after 3 days of injections, the dose is increased by 15 μg until it reaches 60 μg (10 units) with each meal. For patients with type 2 diabetes, the dose is initiated at 60 μg (10 units) and increased to 120 μg (20 units) (Table 1). The dosing difference is based on study findings and the assumption that individuals who are insulin resistant are also amylin resistant.

To reduce the incidence of nausea, patients need to understand that the dose of pramlintide should not be increased if there is any symptom of nausea or gastric upset for at least 3 full days. Some practitioners are advising maintaining the dose for at least a week before increasing to the next dose level, regardless of nausea symptoms.

In studies, patients have reported varying symptoms when they report nausea. Some report nausea, whereas others describe a feeling of fullness. These symptoms can be decreased by advising patients to take the pramlintide with their first bite of food when beginning therapy. Encouraging individuals to be conscious of their feelings of satiety also will help decrease their symptoms of nausea. Overeating tends to lead to a feeling of fullness or nausea. If the satiety effect wears off, patients may take pramlintide up to 15 minutes before the meal.

To reduce the risk of hypoglycemia, the package insert recommends a bolus insulin dose reduction of 50%.[5] For patients whose diabetes is not well controlled at the time of pramlintide initiation, a reduction of 50% may lead to postprandial hyperglycemia. For safety, the bolus insulin dose should be reduced. Initially, it may be best to give the insulin bolus after the meal, considering the potential for early satiety. The bolus insulin is based on the carbohydrates or calories eaten. On initiation, patients are reminded that pramlintide is given with the first bite of food, and insulin is given with the last bite of food.

Patients on an insulin pump may find it helpful to give a dual wave bolus, which would allow them to bolus a portion of the dose with the meal and a portion over 1–2 hours, depending on the type of meal ingested. Self-monitoring of blood glucose (SMBG) is imperative for determining the appropriate bolus doses and adjusting the timing of the insulin bolus, whether injected or delivered with the insulin infusion pump.

Basal insulin may need to be adjusted, depending on the level of glucose control at the time pramlintide therapy is initiated. Questioning patients about their snacking habits may guide whether the basal dose needs to be lowered. Individuals who tend to snack during the day or who eat during the night may need to lower their basal insulin.

SMBG is critical for the successful initiation of pramlintide therapy. It is recommended that SMBG be obtained premeal and 2 hours postprandially until a stable insulin dose is identified. These results should be documented daily with the current pramlinitide dose and bolus insulin dose based on the meal.

Asking patients how they are treating hypoglycemia may identify less-than-optimal treatment habits and allow educators to reinforce more optimal treatment options (i.e., glucose tablets instead of chocolate). It is important to reinforce the appropriate treatment of hypoglycemia (i.e., 15 g of carbohydrate, wait 15 minutes, retest blood glucose, and repeat if necessary). This is also an opportunity to verify that patients with type 1 diabetes have a current prescription for glucagon and someone trained to administer it if needed.

Because pramlintide alters gastric uptake, patients should be cautioned to take oral medications whose maximum concentration or time of onset is important either 1 hour before or 2 hours after eating. These might include certain antibiotics, oral contraceptives, and other medications.

Table 1. Type 1 and Type 2 Diabetes Dosing Titration for Pramlintinde

Titration Guide	Type 1 Diabetes	Type 2 Diabetes
Day 1	15 μg (2.5 units)	60 μg (10 units)
Day 4	30 μg (5 units)	120 μg (20 units)
Day 7	45 μg (7.5 units)	
Day 10	60 μg (10 units)	

Table 2. S.D.'s Seven-Point Glucose Profile Over 1 Year

Time	Fasting (mg/dl)	Breakfast Postprandial	Prelunch (mg/dl)	Lunch Postprandial (mg/dl)	Predinner (mg/dl)	Dinner Postprandial (mg/dl)	3:00 A.M. (mg/dl)
Baseline	158	213	173	136	76	223	124
3 month	55	73	92	77	89	89	109
6 month	79	111	114	145	108	92	110
9 month	54	72	52	114	241	75	88
12 month	227	165	127	89	179	99	51

S.D. faxed his blood glucose levels to the clinic weekly for the first 4 weeks of therapy. He came to the clinic for a follow-up visit at 1 month and every 3 months after initiating pramlintide therapy.

S.D. completed several seven-point profiles during the 18 months that he was enrolled in the pramlintide study (Table 2). He had a decrease in his glucose fluctuations. He also experienced less hypoglycemia and improved awareness of his hypoglycemia. He stated, "I feel better and have more energy. I really like how I feel on pramlintide." Since starting pramlintide, his A1C has improved, his weight is stable, and he has had less hypoglycemia and less fluctuation in his blood glucose levels (Table 3).

Pramlintide is used with insulin for the treatment of type 1 or type 2 diabetes to decrease postprandial glucose fluctuations. It is important to provide appropriate education and medical management when initiating pramlintide.

Clinical Pearls

- Pramlintide can be used in type 1 diabetic patients to reduce the incidence of hypoglycemia.
- Slow titration of pramlintide will reduce the incidence of nausea.
- Decreasing bolus insulin on initiation will reduce the risk of hypoglycemia.
- Frequent phone and face-to-face follow-up is important when titrating pramlintide and insulin doses.

Table 3. S.D.'s Laboratory Data, Weight, and Blood Pressure Readings for 18 Months

	Baseline	6 months	12 months	18 months
Height (inches)	70.5			
Weight (lb)	242	239	241	236
BMI (kg/m^2)	34	33.8	34.1	33.7
Blood pressure (mmHg)	108/74	132/82	—	134/78
A1C (%)	7.4	6.2	6.2	6.8
Cholesterol (mg/dl)	171	—	147	164
LDL (mg/dl)	82	—	81	70
HDL (mg/dl)	78	—	53	82
Triglycerides (mg/dl)	57	—	64	58
Serum creatinine (mg/dl)	1.0	—	—	1.0

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