Low-Dose Glucagon May Prevent Hypoglycemia

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CHICAGO — Nocturnal administration of very-low-dose glucagon appears to prevent hypoglycemia in patients with type 1 diabetes, Dr. Steven V. Edelman reported at the annual scientific sessions of the American Diabetes Association.

Hypoglycemia limits the ability to achieve intensive glucose control among patients with type 1 diabetes. "As we try to intensify control in our patients and as the level of recommended [hemoglobin] A_{1c} keeps getting lower and lower, we face the risk of severe and sometimes fatal hypoglycemia, especially at night. ... Once a patient has had a severe low blood sugar, they're quite afraid to intensify their control," noted Dr. Edelman, professor of medicine at the University of California, San Diego.

And it happens often. In a recent study of 60 patients with type 1 diabetes using continuous glucose monitoring for an average of 12 days, patients experienced 2.1 episodes per day of hypoglycemia (below 70 mg/dL for more than 10 minutes), lasting approximately 1.1 hours each, for a total of 2.3 hours/day. Of those, 60% occurred overnight (Diabetes Care 2005;28:2361-6).

A San Francisco–based company called DiObex Inc. (www.diobex.com), is developing an extended-release injectable formulation of very-low-dose glucagon (VLDG) aimed at reducing or preventing insulin-induced hypoglycemia. In the preliminary studies, however, infusions were used.

"The concept behind VLDG is to infuse just enough overnight to prevent insulin-induced hypoglycemia, but not enough to cause hyperglycemia and deteriorate overall glycemic control," Dr. Edelman said.

He presented findings from a single-center pharmacology study in which six patients with type 1 diabetes treated with insulin pumps underwent 10 separate overnight (10:00 p.m. to 7:00 a.m.) infusions of different doses and durations of VLDG, and also underwent control infusions. The doses were 2, 4, or 8 ng/kg per minute, and the durations were 6, 9, or 12 hours. The patients, four women and two men, had a mean age of 46.2 years and a diabetes duration of 27.8 years. They were in good control, with a mean hemoglobin A_{1c} of 6.52%.

During the control infusions, mean endogenous glucagon levels in the patients ranged from 25 to 50 pg/mL, compared with the normal range of 40-130 pg/mL. During the VLDG infusions, the mean level rose to 80-120 pg/mL with the dose of 8 ng/kg per minute.

The mean amount of time spent in the hypoglycemic range (below 70 mg/dL) ranged from 4% to 16% with the different infusion doses, compared with 30% with the control infusions. Median time spent in hypoglycemia was less than 1% with the infusion doses of 2 and 4 ng/mL per minute and 0% with infusions of 8 ng/mL per minute, versus 14% with the control infusions, Dr. Edelman reported.

Fasting glucose levels at 7:00 a.m. did not exceed 130 mg/dL with the infusion of 2 ng/mL per minute, and only exceeded it with the longest (12-hour) infusion of 4 ng/mL per minute. However, fasting glucose exceeded 130 mg/dL even with the shortest (6-hour) infusion of the 8 ng/mL per minute; most of the patients had a level of around 130 mg/dL, except for the higher dose, he noted. Overall, the patients on VLDG did not have markedly elevated fasting glucoses, compared with the control group. Similarly, median peak glucose levels were around 150 mg/dL in all except during the 12-hour infusion of 8 ng/mL per minute, where it exceeded 250 mg/dL.

No drug-related adverse event of any kind was reported, Dr. Edelman said.

The company plans to proceed next year with a larger trial of longer duration in patients undergoing intensification of insulin therapy. They will receive a single nightly injection of an extended-release formulation, in the home setting.

In a follow-up interview, coauthor Dr. Bernice Welles, vice president of development at DiObex, said VLDG could be considered as long-term therapy. "Since the inability to mount a glucagon response in the face of hypoglycemia that develops after several years of diabetes appears to persist for life, it is not unreasonable to think of our product as chronic replacement therapy. The doses that we expect to bring to market will keep patients in a physiological range of glucagon levels."

Children might particularly benefit, she noted. " There is a very large unmet medical need here. We hear many stories of parents who can't sleep at night for fear of hypoglycemia in their young children." ■