Coverage from the
European Association for the Study of Diabetes (EASD) 2017 Annual Meeting

Minidose Glucagon for Exercise-Induced Hypoglycemia in T1D

Becky McCall

September 18, 2017

LISBON, PORTUGAL — Minidose glucagon is more effective than insulin reduction for preventing exercise-induced hypoglycemia, according to a new study in patients with type 1 diabetes.

"When initiated just before exercise, minidose glucagon is more effective than basal rate insulin reduction for reducing exercise-induced hypoglycemia and may result in less postintervention hyperglycemia than ingestion of carbohydrate," said Michael Rickels, MD, from the University of Pennsylvania, Philadelphia, who presented the results at the European Association for the Study of Diabetes (EASD) 2017 Annual Meeting.

He added, "Minidose glucagon provides a promising new strategy for reducing exercise-associated hypoglycemia."

Explaining the reasons for the study, he said that avoiding exercise-induced hypoglycemia is "a major challenge for people with type 1 diabetes, especially during moderate-intensity aerobic activity. We wanted to see if it [minidose glucagon] better protected individuals from hypoglycemia. Nondiabetic individuals tend to produce glucagon naturally while exercising, but this response is impaired in those with type 1 diabetes."

The 15 adult participants had all had type 1 diabetes for at least 2 years, were using continuous subcutaneous insulin infusion (CSII) (ie, insulin pump) for at least 6 months, and exercised at moderate to vigorous intensity at least three times a week. Mean age was 33 years, mean duration of type 1 diabetes 22 years, six were women, and HbA_{1c} was a mean of 7.1%.

"Such studies are really important for helping us to truly understand the role of glucagon and particularly for the health of type 1 diabetes patients and exercise-related recommendations," remarked moderator Matthew Robinson, PhD, assistant professor, Oregon State University, Corvallis.

Four Partially Blinded Sessions

As well as investigating the effect of subcutaneous minidose glucagon given just prior to exercise, the randomized, four-period crossover study sought to compare results of minidose glucagon administration with no intervention and further to compare glycemic responses with that experienced when participants reduced basal insulin doses or received oral glucose tablets.

Each participant underwent four partially blind study sessions. The four sessions were as follows:

- A glucagon pen (*G-pen Mini*, Xeris Pharmaceuticals) that provided a 150-µg subcutaneous dose of glucagon administered 5 minutes prior to exercise start.
- Glucose tablets of 20 g given 5 minutes prior to start of exercise and followed with a further 20 g at 30 minutes after the start.
- For basal-insulin reduction, the basal rate was decreased by 50% and the participant received a placebo injection 5 minutes prior to exercise start.
- The control procedure involved a sham basal rate reduction and saline injection 5 minutes prior to exercise start.

Study exercise sessions lasted 45 minutes (brisk uphill walking on a treadmill at 50 to 55 VO_{2max}) after which there was a 30-minute recovery period and a standardized meal 75 minutes postexercise start (55% calories carbohydrate, 20% protein, 25% fat as well as an insulin bolus 5 minutes prior to the meal).

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Cite this article: Minidose Glucagon for Exercise-Induced Hypoglycemia in T1D - Medscape - Sep 18, 2017.

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Participants wore a continuous glucose monitor (CGM) that recorded interstitial glucose levels until noon the following day.

They started exercise with just under 7 mmol/L plasma glucose and once exercise started levels decreased in the control and insulin-reduction sessions compared with a modest increase in the minidose glucagon session that remained stable during recovery and a modest increase with the glucose tablets that increased further during recovery.

"A minidose of glucagon given just before aerobic exercise prevented the development of hypoglycemia, while reducing basal insulin at exercise start was not effective in limiting the drop in glycemia during aerobic activity," Dr Rickels said.

"Also, increased carbohydrate intake at approximately 1 g/min for exercise increased hyperglycemia during activity and during the recovery period."

All glucagon levels remained at baseline except for the minidose glucagon group, in which glucagon peaked 30 minutes postadministration, and there was no difference in plasma insulin levels from baseline across any session, reported Dr Rickels.

Hypoglycemia Levels Across Sessions

The proportions of subjects experiencing hypoglycemia varied between groups with around one-third of patients in the control and insulin-reduction arms experiencing hypoglycemia (≤ 3.9 mmol/L (or < 70 mg/dL), seven of 15 in the controls, and seven of 15 in basal-insulin reduction, with a few serious hypoglycemia events (<3.0 mmol/L; one of 15 in the control and two of 15 in the basal reduction), "but nobody in the glucose-tablets or minidose-glucagon groups experienced hypoglycemia," added the researcher.

Two-thirds (11/15) of participants in the glucose-tablets group increased their glucose to ≥10.0 mmol/L (hyperglycemic), with five of 15 above ≥13.9 mmol/L (≥250 mg/dL; serious hyperglycemia). Results from the mini–glucagon-dose group showed that eight of 15 subjects experienced glucose levels at ≥10.0 mmol/L and one of 15 ≥13.9 mmol/L.

"During the recovery period, glucose levels came together and insulin levels after pump administration were similar across all sessions," Dr Rickels noted.

Furthermore, CGM metrics into the next day (midnight to 6 AM on the day postexercise) found no statistically significant differences across the four conditions, including mean glucose level and recurrence of hypoglycemia and durability of hypoglycemia.

The study drug was provided by Xeris Pharmaceuticals. Dr Rickels and Dr Robinson declared no relevant financial relationships.

European Association for the Study of Diabetes (EASD), September 13,12017, Lisbon, Portugal. Abstract 103.

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