Assessment of the Duration of Glucagon's Waning Effect on the Hepatic Glucose Production in Type 1 Diabetes Patients (HEPPI-02)

Simic A, Tschaikner M, Jungklaus M, Tuca AC, Pieber TR, DeVries JH, Regittnig W

Objective: The goal of the study was to assess the duration of glucagon's waning effect on the hepatic glucose production and the blood glucose concentration in type 1 diabetes patients.

Methods: Five people with type 1 diabetes came to the clinical research center on four study days spaced 1-3 weeks apart. On the study days, each subject received two subcutaneous boluses of glucagon (0.50 mg) separated by either 4 hours (Day A), 8 hours (Days B and D), or 12 hours (Day C). On study days A, B, and C the subjects continued their fasting between the two glucagon administrations whereas on study day D they were requested to consume a liquid meal (82 g carbohydrates) midway between the two subcutaneous glucagon injections. To determine the rates of glucose production after the glucagon administration, a stable glucose tracer ([6.6-$^2H_2$]glucose) was infused intravenously at variable rates. Also, blood was frequently sampled throughout the experiments to measure glucose and tracer glucose concentrations as well as plasma glucagon and insulin levels.

Results: Ten people with type 1 diabetes (3 women and 7 men) were invited to take part in the study. Of these, 3 were excluded due to screening errors and 2 dropped out of the study prematurely due to adverse events (nausea and vomiting after glucagon administration). The 5 subjects who completed the study (5 men) had a mean ± SD age of 32.3 ± 5.8 years (range 24-40 years) and a mean ± SD body mass index of 24.9 ± 2.4 kg/m^2 (range 21.3 -28.0 kg/m^2). Their mean ± SD diabetes duration was 24.8 ± 9.7 years (range 12 - 37 years), and their mean ± SD HbA1c level was 63 ± 6 mmol/mol (7.9 ± 0.5 %; range 53 - 69 mmol/mol [7.0 - 8.5 %]). It was found that the average ratios (means ± SE) between the increases in the area under the plasma glucose curve observed for 90 minutes following the second glucagon administration (AUC_{PGBol2}) and that observed for 90 minutes following the first glucagon administration (AUC_{PGBol1}) did not differ between the study days with a break interval of 4 hours (70.1 ± 5.3 %), 8 hours (78.2 ± 3.3 %) and 12 hours (73.8 ± 4.0 %) and the study day with a break interval of 8 hours and a liquid meal between the two glucagon administrations (76.5 ± 2.0 %) ($p > 0.520$, with repeated-measures ANOVA). Similarly, the average ratios between the increases in the area under the hepatic glucose production curve observed for 90 minutes following the second glucagon administration and that observed for 90 minutes following the first glucagon administration did not differ between the 4 study days.

Conclusions: These data suggest that the waning of glucagon's effect on the hepatic glucose production may not be influenced by carbohydrate ingestion and/or the length of the time interval between two successive glucagon administrations.