

American Diabetes Association Meeting
67th Scientific Sessions
June 22-26, 2007

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Abstract: Nocturnal Administration of Very Low Dose Glucagon in Patients with Type 1 Diabetes Reduces Episodes of Nocturnal Hypoglycemia

Background: Nocturnal hypoglycemia (HG) is a frequent complication in patients with type 1 diabetes (T1DM). While glucagon normally plays a key counter-regulatory role, patients with T1DM for >5 -10 years typically lack a glucagon secretory response in the face of HG. We hypothesized that nocturnal administration of Very Low Dose Glucagon (VLDG) would decrease nocturnal HG in subjects with T1DM.

Methods: A single-center, single-blind controlled trial was conducted in 6 subjects aged 18 -55 with T1DM for ≥ 10 years, HbA1c $\leq 8.0\%$, and BMI ≤ 25.5 kg/m² using insulin pumps. Subjects underwent 10 nocturnal studies during which their insulin pumps were used to administer their usual basal rate of insulin and VLDG was administered as a continuous SC infusion via Animas pump starting at 2200h. Each subject, in random fashion, underwent a single control (3% mannitol) infusion for 12 hours or VLDG doses of 2, 4 and 8 ng/kg/min; each dose was infused for 6, 9 or 12 hours on separate evenings. Glucose and glucagon levels were measured at least hourly. Subjects also underwent continuous glucose monitoring (CGM) (Medtronic) throughout infusion periods and the following day. HG was defined as a glucose ≤ 70 mg/dL (≥ 10 minutes with CGM).

Results: Mean glucagon levels during the control infusion ranged from 25 - 50 pg/mL (ref. range 50-150 pg/mL) and rose gradually after the 0730h breakfast. During VLDG treatment, glucagon levels rose in a dose dependent fashion; mean levels achieved during the 8 ng/kg/min infusions were in the 80 to 120 pg/mL range. During control infusions, subjects spent 29.9% of their time (2200-0700h) with HG compared with 4 to 16% when treated with 4 or 8 ng/kg/min. Episodes/hour of HG decreased by 78% in the 8 ng/kg/min group as compared with the control infusion (.027 vs. 0.12). Fasting glucose (FG) levels increased in a dose-dependent fashion, as well as by duration within each dose group. FG level in the control group was 86 mg/dL compared with 102 and 136 in the 6-hour 4 and 8 ng/kg/min infusions. There were no drug related adverse events.

Conclusions: VLDG appears to prevent nocturnal HG in T1DM and will be studied in longer placebo-controlled trials. Patients striving to achieve tight glycemic control may experience fewer, less severe episodes of nocturnal HG when treated with VLDG.