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FACT SHEET

Graded Glucose Infusion for Assessment of β-Cell Function

General Uses and Considerations

The graded glucose infusion technique provides a sensitive assessment of insulin secretory capacity and β-cell responsiveness. In brief, serum insulin and C-peptide responses to a stepped incremental intravenous glucose infusion are measured in order to determine dose-response relationships with blood glucose.

The technique generates valuable insulin-glucose dose-response data over a range of plasma glucose concentrations relevant to normal physiology and the pathophysiology, i.e. states of glucose intolerance (impaired glucose tolerance; impaired fasting glucose) and type 2 diabetes. Paired studies in individual subjects permit changes in β-cell responsiveness to therapy, e.g. an incretin mimetic or an insulin secretagogue, to be quantified. The graded glucose infusion is suitable for studies in non-diabetic subjects, and subjects with glucose intolerance or type 2 diabetes.

Subjects and Preparation

Subjects are studied in the morning after an overnight fast. Admission prior to the clinical research facility ahead of the procedure helps ensure compliance with nutrition and exercise prescriptions; it also helps acclimate the subject to the clinical research environment. For patients with diabetes, an overnight variable rate intravenous infusion may be used to standardize blood glucose levels on the morning of the clamp procedure.

Procedure

After an overnight fast a basal (control) period is followed by sequential incremental intravenous infusions of glucose calculated to raise the blood glucose concentration from fasting levels to the hyperglycemic range (approximately 300 mg/dL,17 mmol/L).

A graded infusion of 20% glucose is administered at 2, 4, 6, 8, and 12 mg/kg/min each for 30 minutes. Blood samples are drawn at 10, 20, and 30 minutes during each 30-minute period for measurement of glucose, insulin, and plasma C-peptide.

Interpretation

Pre-hepatic insulin secretion rates (ISR, in pmol/kg/min.) are derived by deconvolution of peripheral C-peptide concentrations using a two-compartment model of C-peptide kinetics and population-based C-peptide kinetic parameters.

The mean insulin secretion rate at the end of each glucose infusion step is plotted against mean blood glucose to generate a dose-response curve for β-cell function. Changes in the relationship between glucose and insulin secretion rate, e.g. as a result of an intervention that improves β-cell function, can be identified as shifts in the mean dose-response curve which are amenable to statistical analysis.

The graded glucose infusion technique can be used to examine the dose-response effects of an incretin mimetic, e.g. a glucagon-like peptide-1 agonist, on β-cell function (Figure 1) since this does not involve activation of the intestinal incretin system. Since delivery of glucose is intravenous rather than oral it is not possible to directly quantify the contribution of the endogenous incretin system to postprandial glucose-stimulated insulin secretion. The latter can be assessed using an oral glucose or mixed meal challenge (see fact sheet).

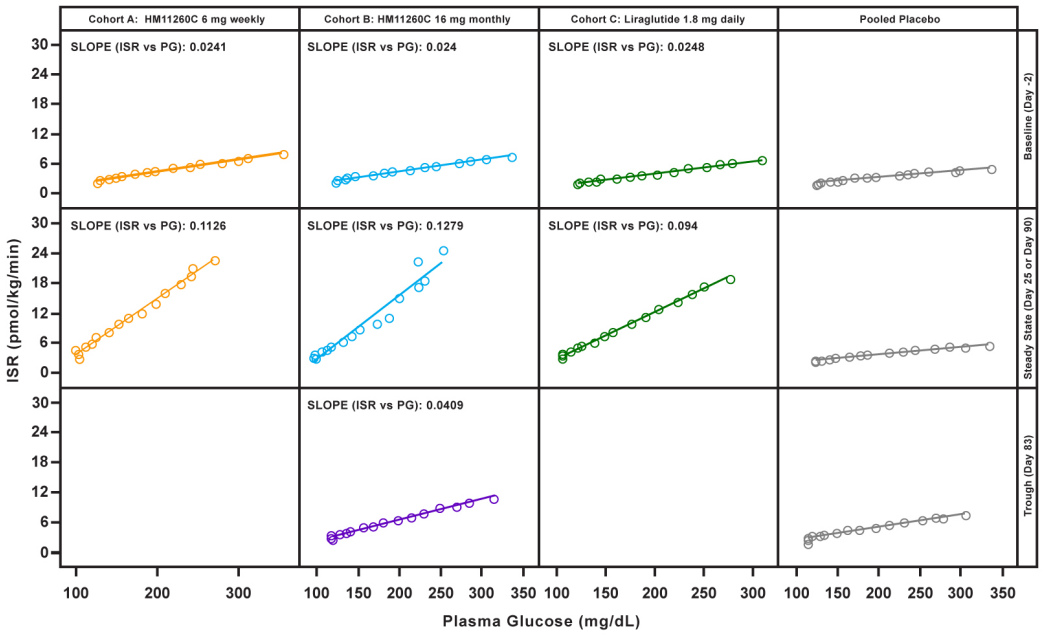

Figure 1: Insulin secretion rate vs. plasma glucose assessed using the graded glucose infusion technique pre- and post-treatment for two regimens of HM11260C, a novel long-acting form of CA Exendin-4 (an exendin-4 analog), i.e. 6 mg weekly (Cohort A) or 16 mg monthly (Cohort B at peak and trough drug levels), liraglutide 1.8 mg daily (Cohort C), and placebo in metformin-treated subjects with type 2 diabetes. The change in the slope post-treatment was statistically significant for all active treatments. Data from Hompesch M et al. Data presented at the American Diabetes Association 75th Scientific Sessions. Boston.

Advantages of the Graded Glucose Infusion Technique

- Sensitive and reproducible method for the assessment of β-cell function and the effect of novel diabetes therapies
- Provides robust data about drug-induced changes in insulin secretion over the physiological and pathophysiological range
- Changes in the relationship of insulin secretion rate vs. plasma glucose reflect β-cell responsiveness to glucose

References and Further Reading

Byrne MM, Sturis J, Polonsky KS. Insulin secretion and clearance duringgraded glucose infusion. Am J Physiol 1995;268:E21–E27, 1995

Hovorka R, Koukou E, Southernden D, Powrie JK, Young MA. Measuring prehepatic insulin secretion using a population model of C-peptide kinetics: accuracy and required sampling schedule. Diabetologia 1998;41:548–554.

Krentz AJ, Heinemann L, Hompesch M. Assessment of β-cell function. In: Krentz AJ, Heinemann L, Hompesch M (Eds). Translational Research Methods for Diabetes, Obesity, and Cardiometabolic Drug Development: Focus on Early Phase Studies. Springer 2015.

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