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FACT SHEET

Hypoglycemic Clamp Studies

General Uses and Considerations

The hyperinsulinemic hypoglycemic clamp is a variant of the glucose clamp technique designed to assess counterregulatory hormone responses under standardized conditions of experimental hypoglycemia.

Hypoglycemic clamps have been extensively used in studies of the pathophysiology of iatrogenic hypoglycemia. They are also used to study the effects of novel therapies intended to reverse or prevent hypoglycemia, e.g. novel formulations of glucagon, anti-insulin receptor antibodies. Similarly, the effects on glucose counter-regulation of glucose-lowering drugs that on theoretical grounds might impair the physiological response to hypoglycemia, e.g. by restraining increases in hepatic glucose production, can also be studied with a high degree of precision and reproducibility (Figure 1). Such precision is not possible using a bolus of insulin which would cause non-standardized and unpredictable reductions in blood glucose to potentially unsafe levels.

To perform a hypoglycemic clamp individualized intravenous insulin and glucose infusions are titrated to achieve and maintain a pre-defined blood glucose target for a specified period of time, e.g. 30-60 min, at euglycemic and then hypoglycemic target levels. For example, 125, 90, 70 and 55 mg/dL (approximately 7, 5, 4 and 3 mmol/L). During each glucose plateau blood samples are collected to assess variables of interest, e.g. glucose, insulin, C-peptide (where appropriate), and counterregulatory hormones (catecholamines, glucagon, cortisol, growth hormone). At the end of the lowest clamp target level the intravenous insulin infusion is terminated.

Subjects and Preparation

The subject is fasted >8 hours overnight. Limitations are placed on factors such as strenuous exercise, alcohol, caffeine and tobacco use which may influence physiological responses to insulin. Overnight admission to the clinical research facility prior to the clamp procedure helps ensure compliance with nutrition and exercise prescriptions as well as helping 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 prior to commencement of the hypoglycemic clamp. Care must be taken to exclude diabetic subjects with a history of recurrent hypoglycemia, hypoglycemia unawareness, evidence of cardiovascular disease or major microvascular complications, e.g. advanced diabetic retinopathy.

Procedure

Controlled hypoglycemia is most reliably achieved an automated glucose infusion system (Biostator®). Hyperinsulinemia is achieved using a continuous intravenous infusion of soluble human insulin or a rapid-acting insulin analog. Plasma glucose is measured every minute and an infusion of 20% glucose is adjusted automatically by a validated algorithm to maintain euglycemia. The Biostator program is then set to the pre-specified plateau(s) of hypoglycemia. On completion of the hypoglycemic clamp the insulin infusion is terminated and blood glucose is permitted to rise spontaneously. In order to avoid prolonged hypoglycemia, a reversed clamp may be applied as an additional safety feature (Figure 1). The subject is carefully monitored during the entire procedure by medical staff.

Theoretical and Practical Considerations

Normal non-diabetic subjects are exquisitely sensitive to small decrements in plasma glucose; levels within the normal range cause suppression of endogenous insulin secretion at approximately 70 mg/dL (4.0 mmol/L). As glucose levels decline, activation of glucagon and epinephrine secretion is triggered. The glucose threshold for counterregulatory hormone release is modified by factors, including age, sex, plasma insulin concentration, and antecedent episodes of hypoglycemia. If blood glucose continues to fall towards approximately 55 mg/dL (3.0 mmol/L) the hormonal response is intensified and classic neuro-adrenergic symptoms of hypoglycemia are generated.

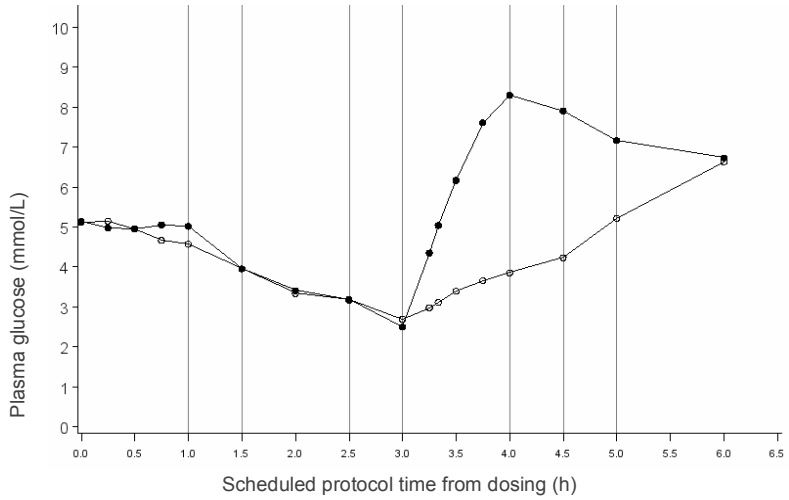

Figure 1: Mean plasma glucose concentration during a stepped hyperinsulinemic hypoglycemic clamp for a glucokinase activator (AZD1656) alone (open circles) and AZD1656 + glucagon studies (solid circles). The hypoglycemic clamp was released at 3 hours (arrow). On the AZD1656 + glucagon study day glucagon 1 mg was given at 3.0 hours by intramuscular injection. The vertical lines indicate the time periods for the preset target plasma glucose levels of the \ clamp (5.0, 4.0, 3.2 and 2.7 mmol/L; 90, 72, 58 and 49 mg/dL) and of the subsequent reversed clamp. Data from Krentz et al. 2014.

Interpretation

The hypoglycemic clamp permits the onset of secretion and the magnitude of counterregulatory hormone responses to be quantified under standardized and reproducible conditions. On termination of the hypoglycemic clamp the time to spontaneous recovery to euglycemia can be captured as an additional outcome variable. Validated questionnaires may be used to identify glycemic thresholds for hypoglycemic symptoms.

Advantages of Hypoglycemic Clamp Studies

- Standardized reproducible hypoglycemic stimulus to counterregulatory hormone release
- Safe and generally well tolerated

References and Further Reading

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855 3rd Avenue Suite 3340
Chula Vista, CA 91911. USA
bd@prosciento.com - www.prosciento.com