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. The hyperinsulinemic hypoglycemic clamp has been extensively used in studies of the pathophysiology of iatrogenic hypoglycemia. It is 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. Glucose-lowering drugs that on theoretical grounds could 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. This precision is possible using a bolus of insulin which would cause non-standardized reductions in blood glucose to potentially unsafe levels.

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 hypoglycemic target levels. For example, 125, 90, 70 and 55 mg/dL (approximately 7, 5, 4 and 3 mmol/L). During each plateau blood samples are collected to assess variables of interest, e.g. glucose, insulin, C-peptide (if 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 strenuous exercise, alcohol, caffeine and tobacco use, all of which may influence responses to insulin. Overnight admission prior to the clamp procedure helps ensure compliance with nutrition and exercise prescriptions and helps acclimate the subject to the clinical research environment. For patients with diabetes, an overnight intravenous infusion may be used to standardize blood glucose levels prior to commencement of the hypoglycemic clamp. Care must be taken to exclude subjects with a history of recurrent hypoglycemia, hypoglycemia unawareness, or evidence of cardiovascular disease.

Procedure

Controlled hypoglycaemia is most reliably achieved an automated glucose infusion system (Biostator). Hyperinsulinemia is achieved using a continuous 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 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 hormone release is modified by multiple 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 symptoms of hypoglycemia are generated.

Interpretation

The onset of secretion and the magnitude of counterregulatory hormone responses can 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 graded glucose infusion

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

References and Further Reading


ProSciento Methodology Fact Sheets