prosciento®

ADVISE • ADVANCE • ACHIEVE

FACT SHEET

Introduction to Glucose Clamps: Automated Versus Manual Techniques

The glucose clamp technique in its various forms is a well-established tool in clinical metabolic research and diabetes drug development. Both the U.S. and European regulatory authorities consider euglycemic clamps to be the 'gold standard' for assessing the efficacy of novel insulins. The hyperinsulinemic euglycemic clamp technique has a key role in testing novel insulin-sensitizing drugs.

In essence, the glucose clamp technique permits the blood glucose concentration of a study subject to be adjusted and maintained at a predetermined level. Exogenous glucose is delivered at a variable rate guided by frequent measurements of blood glucose at the bedside. Variants of the technique include the euglycemic or isoglycemic clamp, hyperinsulinemic euglycemic clamp, the stepped hypoglycemic clamp, the islet cell or pancreatic clamp, and the hyperglycemic clamp. ProSciento scientists have been closely involved in developing glucose clamp methodology over several decades. More than 1,000 clamp procedures are performed annually at ProSciento's specialized clinical research unit (CRU) in Chula Vista, California.

Patient Preparation

Typically the study participant is studied in the morning following an overnight fast of >8 hours. Admission to the clinical research facility the day before the procedure helps minimize the potential for the confounding effects of changes in nutritional status and exercise levels. For patients with diabetes, an overnight variable rate intravenous infusion of insulin may be used to standardize fasting blood glucose concentrations in advance of a clamp study. Prior to the commencement of the clamp intravenous lines are placed for the infusion of glucose (and insulin along with other hormones, if required – see islet cell clamp below) and for venous sampling. Glucose is measured in blood that is 'arterialized' by warming the limb to open arterio-venous channels thereby reducing glucose extraction by insulin-sensitive tissues.

Glucose Clamp Applications

Major glucose clamp applications in clinical metabolic research include:

- Determining time-action profiles of novel insulin analogs and alternative insulin delivery routes (euglycemic or isoglycemic clamp)
- Measuring whole-body insulin sensitivity and the response to insulin-sensitizing drugs (hyperinsulinemic euglycaemic clamp)
- Assessing endogenous insulin secretion and the β-cell response to secretagogues (hyperglycemic clamp)
- Providing a standardized hypoglycemic stimulus to counterregulatory hormone production (stepped hypoglycemic clamp)
- Inhibiting endogenous hormone secretion and replacing insulin, glucagon, and growth hormone (pancreatic or islet cell clamp)
- Assessing endogenous insulin secretion and the β-cell response to secretagogues (hyperglycemic clamp)

The glucose clamp technique can be used to rapidly attain the required blood glucose level and maintain it at target according to the objectives of the experiment. Ancillary techniques such as isotopic tracer methodology or indirect calorimetry can be combined with a clamp to provide additional information about substrate utilization.

In the context of glucose clamp studies, deviations in blood glucose from the pre-specified target are undesirable. Thus, when evaluating clamp services provided by a clinical research organization the accuracy with which the blood glucose concentration is maintained at target becomes an important quality consideration. While no universal definition of clamp quality has been established a coefficient of variation of <5% is regarded as optimal.

There are two major approaches to performing glucose clamp studies:

Manual Glucose Clamp Studies

Unless otherwise specified, it should be assumed that manual glucose clamp methodology is being employed. Manual glucose clamps are open-loop systems that comprise measurement of blood glucose at the bedside and estimation of the glucose infusion rate required to reach and maintain the glucose target guided by the human clamp operator. While the manual clamp method is versatile the skill of the operator is a factor in the quality of each clamp study. There is a well-recognized learning curve associated with acquiring the requisite expertise for high quality, reproducible clamp studies. This brings the potential for variability between individual clamp operators. This consideration is especially important when change from baseline in response to a therapeutic intervention is measured.

Automated Glucose Clamp Studies

An alternative technique developed and applied by ProSciento scientists is the automated glucose clamp. This specialized approach utilizes a closed-loop system in which the variable of inter-operator proficiency is removed. The automated glucose clamp technology determines, and in a closed-loop or semi closed-loop setting infuses, the required amount of exogenous glucose to maintain the target glucose level. A published algorithm calculates glucose requirements based on glucose measurements obtained minute-by-minute or at five-minute intervals, depending on the particular technology employed. In this scenario, the operator is not required to make frequent judgments about the glucose infusion rate required to maintain the target glucose concentration. Thus, the potential for unconscious human operator bias is largely eliminated along with the issue of inter-operator variability.

Advantages of ProSciento's automated glucose clamp methodology include:

- Algorithm driven glucose infusion rates
- Deviation from blood glucose target less than 5%
- Stable blood glucose level over a wide range (50 to 550 mg/dl)
- Blood glucose measurements in tight, consistent one or five-minute intervals

Throughput advantages include:

- Ability to perform 15+ separate procedures simultaneously
- Ultra-long glucose clamp procedures of 36 hours or longer
- Clamp results immediately ready for data processing (no manual data entry)

Contact us at bd@prosciento.com to learn more about glucose clamp studies for metabolic drug and device development.

prosciento®
ADVISE • ADVANCE • ACHIEVE
855 3rd Avenue Suite 3340
Chula Vista, CA 91911. USA
bd@prosciento.com - www.prosciento.com