Expediting Antidiabetic Drug Development Using Glucose Clamps

A Heavy Burden
The pharmaceutical industry is responding to fiscal and ethical pressures to expand the scope of early phase clinical research to incorporate signals of efficacy. This empowers better decision making earlier in the drug development process, which may prevent unnecessary investment and study participant exposure to drugs that fail to exhibit a therapeutic benefit.

Challenges in Antidiabetic Drug Development
A risk mitigation strategy is particularly critical in developing treatments for diabetes which face the additional expense and burden of exploring treatment-related cardiovascular risk during late phase development. Deferring investigations for signals of both glycemic efficacy and cardiovascular risk to late phase is overly treacherous and not a sustainable model for antidiabetic drug development.

Work Smarter Not Harder
Pharmacodynamic models may provide compelling evidence of glycemic efficacy to warrant advancing a drug candidate into late phase development. Glucose clamps are pharmacodynamic models used to develop treatments for diabetes. Although the name conjures images of fastening devices, glucose clamps are infusion based procedures that provide comprehensive solutions for studying glucose dysregulation. Glucose clamp data may provide mechanistic clues about a drug’s activity as well as support interpretations of efficacy. They are recognized as the gold standard for measuring insulin or beta-cell sensitivity, and are used to characterize the time-action profiles of insulin products.

Interrupting the Glucose-Insulin Feedback Loop
Under normal physiological conditions, insulin and glucose simultaneously interact and inversely influence each other’s concentrations. In order to directly investigate the impact of these substrates on each other, one of these variables must be held constant. This is achieved through the glucose clamp. During glucose clamps, this feedback loop is interrupted.
How Sweet
The participant’s blood glucose is frequently monitored and used to make adjustments to a variable infusion of glucose in order to maintain a blood glucose target. That blood glucose target may be defined as:

- **Euglycemic**: Blood glucose levels typical of a fasting healthy person.
- **Hyperglycemic**: Blood glucose levels above what would be typical for a fasting healthy person.
- **Hypoglycemic**: Blood glucose levels below those typical of a fasting healthy person.
- **Isoglycemic**: Fasting blood glucose levels typical for the population being studied.
- **Isoglycemic in Type 2 diabetics**: Target blood glucose level that would clinically be considered hyperglycemic for fasting healthy populations. Isoglycemic clamps in healthy participants would also be euglycemic.

It Takes All Kinds
There are many different types of clamps, each with its own specific application. For example, in the case of a hyperinsulinemic clamp, insulin is infused to stimulate peripheral uptake of glucose as well as suppressing endogenous insulin and glucose production. This allows the calculation of the participant’s whole body glucose disposal rate. If this type of clamp is performed in populations with sufficient insulin resistance, endogenous glucose production may not be fully suppressed by the induction of hyperinsulinemia. The addition of a stable glucose isotope allows for the quantification of residual endogenous glucose production so the whole body glucose disposal rate may be accurately represented.

In the case of a hyperglycemic clamp an infusion of dextrose raises the blood glucose, stimulating endogenous insulin secretion. The target hyperglycemia is maintained by variably adjusting the glucose infusion to counteract the increased circulating levels of insulin. These data can be used to measure the amount of glucose metabolized, quantify beta-cell response, and independently examine early and late phase insulin secretion.

Time-Action Profile clamps are used to characterize insulin products. During these clamps the insulin product under investigation is administered and a variable infusion of dextrose applied to maintain the glycemic target.

**Fig 3. Competent Authorities and Time-Action Profile Clamps**

**Competent Authorities and Time-Action Profile Clamps**

- **FDA**: In the case of a new insulin with perhaps unique pharmacokinetic characteristics dictating a specific method of use […], efficacy can be assumed based on pharmacodynamic (e.g., clamp) studies.

  Guidance for Industry – Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention FDA/CDER, Feb 2008

- **EMEA**:3.3.1 pharmacodynamic data […] data on the time-action profiles using the euglycaemic clamp technique should be available, providing data based on the glucose infusion rate and the exogenous insulin serum concentration.

  EMEA/CPMP note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus LONDON, 30 May 2002, CPMP/EWP/1080/00
Repeat After Me

The glucose clamp is exquisitely reproducible. It has a reported intraindividual coefficient of variation of ~10%. Other mathematically modeled indices of insulin sensitivity exhibit ~20-30% intraindividual coefficient of variation. This translates into greater confidence that observed treatment effects are due to the study intervention and not to the inherent variability of the test. Additionally, this more sophisticated testing method can detect treatment effects in smaller populations of the magnitude studied in early phase research. This affords an opportunity for accelerated development through early signals of efficacy.

Further Reading