Methodology fact sheet: Hypoglycemic glucose clamp studies

Why perform hypoglycemic glucose clamp studies?

- → To establish the blood glucose recovery time and profile after insulin-induced hypoglycemia
- → To understand the effects of a trial drug on counter-regulatory hormones after insulin-induced hypoglycemia
- → To assess the effects of a trial drug on hypoglycemic symptoms occurring with a stepped hypoglycemic clamp

Investigating counter-regulatory mechanisms to hypoglycemia

Counter-regulatory measures are activated at blood sugar levels just below the euglycemic range (< 70 mg/dl). They involve glucagon, which is secreted by the pancreatic alpha-cells, stimulates hepatic glycogenolysis and promotes gluconeogenesis; and epinephrine, which stimulates hepatic glycogenolysis, mobilizes precursors for hepatic and renal gluconeogenesis, and limits glucose utilization by insulin-sensitive tissues. These measures should prevent plasma glucose levels falling below 50–55 mg/dl, which would cause neurogenic and neuroglycopenic hypoglycemic symptoms or even brain dysfunction.

These counter-regulatory mechanisms are tightly controlled and effective in healthy people. However, people with diabetes often have hypoglycemia unawareness with inefficient counter-regulatory measures. This puts the body at risk of severe hypoglycemia. Investigating bodily responses and potential countermeasures is essential to inform the development and improvement of acute rescue interventions and ongoing treatments that shorten the time spent in a hypoglycemic state.

How does the hypoglycemic glucose clamp work?

At Profil, we use our proprietary automated clamp device, ClampArt®, to assess the counter-regulatory mechanisms to hypoglycemia. Subjects receive a continuous intravenous insulin infusion to reach the target glycemic levels (typically 45–50 mg/dl). After the target level has been reached, glucose infusion is used to avoid further lowering of blood glucose levels. Blood samples are taken at this level to determine changes in counter-regulatory hormone concentrations. A visual analog scale (VAS) is simultaneously used to assess the hypoglycemic symptoms and rate their intensity.

After a fixed time in a hypoglycemic state, the blood glucose is allowed to increase to the euglycemic range. The time required to reach the 54 mg/dl and 70 mg/dl marks is an important measure of counter-regulation efficiency.

How can risk to the patient be avoided?

There are risks associated with putting subjects into a hypoglycemic state. Profil's ClampArt is designed to address this risk. It automatically checks the subject's blood glucose 12 times per minute and adjusts the infusion rates once per minute. Typically with a manual clamp, blood glucose is only checked once every 5 minutes. The automated ClampArt-based method ensures that the hypoglycemic state is tightly controlled and there is little risk to the subject's health.

Key hormones

The key counter-regulatory hormones are glucagon, epinephrine, cortisol and growth hormone.

Hypo- vs. hyper-

Hypoglycemic clamps are used to assess counter-regulation, while hyperglycemic clamps are needed to assess pancreatic beta-cell function.

Did you know?

Profil has carried out over 25,000 clamp experiments — that's more than any other institution in the world.

Advantages of hypoglycemic clamp studies

This is the global standard method for studying counter-reactions to hypoglycemic events.

Challenges of hypoglycemic clamp studies

Study submissions to regulatory agencies require evidence of high experimental quality with blood glucose levels very close to the hypoglycemic target and proper oversight. Without this evidence, the study data may be rejected. Repetitions of hypoglycemic clamp runs should be avoided for ethical as well as financial reasons. Putting subjects into a hypoglycemic state is not without risk.

Therefore, this method should only be carried out at institutions with considerable experience, such as Profil.

Further reading

1. Hövelmann, U., et al. 2019. Low doses of dasiglucagon consistently increase plasma glucose levels from hypoglycaemia and euglycaemia in people with type 1 diabetes mellitus. Diabetes Obes. Metab. 21(3): 601–610.
2. Hövelmann, U., et al. 2018. Pharmacokinetic and pharmacodynamic characteristics of dasiglucagon, a novel soluble and stable glucagon analog. Diabetes Care 41(3): 531–537.
3. Heise, T., et al. 2004. Effect of pramlintide on symptom, catecholamine, and glucagon responses to hypoglycaemia in healthy subjects. Metabolism 53(9): 1227–1232.

Profil: the leading CRO for metabolic research
Profil Institut für Stoffwechselforschung GmbH
Hellersbergstr. 9
41460 Neuss (near Düsseldorf)
Germany

Phone: +49 21 31 40 180
Email: contact@profil.com

www.profil.com

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