

New Insulins

Scientific and technical advances in recent years have driven the development of a number of human and analogue insulins with better clinical and pharmacological properties **Dr Victoria Stokes**, Specialist Registrar in Diabetes and Endocrinology, and **Stephen Gough**, Professor of Diabetes and Consultant Physician, at the Oxford Centre for Diabetes, Endocrinology and Metabolism review the new insulins

While animal insulins are still available, and preferred by some people, most patients are now using human and analogue basal and rapid-acting insulin therapy as individual injections or as a mixture in the same delivery system. An increasing number of people with Type 1 diabetes are also using rapid-acting analogue insulins via continuous subcutaneous insulin infusions.

What are we aiming for?

The ideal basal insulin should help normalise fasting blood glucose values, with no hypoglycaemia, by providing stable suppression of hepatic glucose production between meals with no significant peaks or troughs and no injection-to-injection variability. Preferably, there should also be no unwanted weight gain. Efforts to achieve these characteristics have focused on modifying human insulin in a variety of ways to reproducibly prolong absorption and to allow the duration of action to overlap with the next dose. Many people also want to reduce the frequency of their injections to at once a day, or even less.

The ideal rapid-acting insulin should also protect against post-prandial glucose excursions, without unwanted and limiting side effects – the most important of which is hypoglycaemia. Although some rapid-acting insulins are licensed for use immediately before, during, or even after, a meal, the delay in absorption from the subcutaneous depot into the circulation usually requires injection of a calculated insulin dose before meals to allow the rise in insulin concentration and its metabolic action to appropriately match increasing plasma glucose levels. Ongoing development programmes continue to deliver novel insulins which aim to get closer to the ideal insulin.

Insulin degludec

Insulin degludec, a long-acting basal insulin for use in Type 1 and Type 2 diabetes, consists of human insulin modified through the addition of an acetylated ligand¹. The addition of phenol causes degludec to adopt a stable dihexameric (multi-molecular) state *ex-vivo*. After injection into subcutaneous tissue, the phenol rapidly diffuses away, allowing insulin degludec to link into chains of multi-hexamers, linked by a contact between the zinc core of one molecule and the fatty acid group of its neighbour. As the zinc diffuses away, there is a slow release of insulin monomers which can then be absorbed into the circulation, with a terminal half-life of approximately 25 hours at steady state, compared with around 12.5 hours for insulin glargine.

In treat to target clinical studies, similar glycaemic targets can be achieved, generally, with fewer episodes of

confirmed 24 hour and nocturnal hypoglycaemia, compared with existing basal insulin analogues². Studies have also demonstrated that varying the injection timing of insulin degludec does not compromise glycaemic control or safety, even at the extremes of dosing intervals of 8 to 40 hours.

Insulin degludec does not appear to be affected by renal impairment and may be of benefit in patients undergoing haemodialysis. Similarly, there appears to be no significant difference in absorption or clearance between subjects with varying degrees of hepatic impairment.

Insulin degludec is also available as a U200 preparation in which it is twice as concentrated as U100. The 50 per cent reduction in volume for each unit of insulin allows patients to inject up to 160 units in a single injection from a pre-filled, disposable pen device³.

Insulin degludec has been approved for use in the UK and other European countries, although the Food and Drug Administration in the US has requested further data on cardiovascular safety.

Glargine U300

Although the essential structure and method of action is similar to that of glargine U100, the U300 formulation of insulin glargine provides 300 units per ml and represents a more concentrated formulation of a well-established basal insulin. The more concentrated version leads to a reduced volume of about two-thirds and a reduced depot surface area of about 50 per cent. This results in a reduced rate of release of insulin from the depot, a flatter pharmacokinetic profile and an increase in the terminal half-life over insulin glargine U100⁴. As with insulin degludec, this new high strength formulation has been designed to address the needs of patients requiring large doses of insulin.

Insulin glargine U300 is currently under evaluation as part of the Phase III EDITION programme, including studies in people with Type 1 and Type 2 diabetes. Preliminary data in Type 2 diabetes show non-inferiority compared with insulin glargine U100, with respect to glycaemic control and reduction in HbA1c, but with lower rates of hypoglycaemia, particularly at night, without any increase in adverse events⁵.

PEG lispro

PEG lispro is a long-acting insulin comprised of modified insulin lispro. A polyethyleneglycol (PEG) group is added enabling each monomer to bind three molecules of water and increasing its hydrodynamic diameter. This large functional molecular size reduces renal clearance and slows absorption from subcutaneous tissues, thus prolonging its half-life. It also appears to alter its tissue distribution with

some degree of hepatic selectivity. Pharmacokinetic and pharmacodynamic studies suggest fairly stable and flat serum concentrations for around 48 hours, a duration of action of at least 36 hours and coupled with a low rate of intra-subject variability.

Phase II trials have demonstrated non-inferiority in glucose-lowering properties when compared with insulin glargine, with reduced variability, reduced nocturnal hypoglycaemia and the unexpected benefit of modest weight reduction^{6,7}. Pooled analysis of two trials has demonstrated that this weight loss is independent of body mass index, not related to gastrointestinal side effects and not related to hypoglycaemia. PEG lispro treatment was, however, associated with transient increases in liver transaminases (but within the normal range), and an adverse effect on lipid profile (increased LDL and decreased HDL) in most patients. PEG lispro is currently undergoing evaluation in Phase III trials.

IDegAsp

IDegAsp, a fixed combination of insulin degludec and insulin aspart, has been given with the evening meal in clinical trials and has been shown to reduce postprandial glucose excursions, with less nocturnal glycaemia when compared with insulin glargine⁸. Mean daily insulin doses and increase in body weight were similar between the two treatment arms. IDegAsp compares favourably to insulin aspart 30 in achieving comparable glucose-lowering effects, with less nocturnal hypoglycaemia and a lower mean two hour post-dinner plasma glucose⁹.

Ultra-rapid insulin analogues in development

Although developments in rapid-acting insulins are ongoing, novel formulations appear to be some way off. Phase III trials are, however, underway for the new, ultra-rapid acting insulin, FIAsp. This new preparation is, in essence, insulin aspart, but with the additional excipients nicotinamide and arginine. These additions appear to increase the onset of action of FIAsp, with early data suggesting that tolerability and adverse events, namely hypoglycaemia, are similar to those found with insulin aspart.

Meanwhile, BIOD-238 and BIOD-250 are two ultra-rapid acting insulin analogues, derived from modified insulin lispro, currently undergoing Phase I trials. Preliminary results have demonstrated significantly more rapid absorption rates, with double the total amount of insulin absorbed in the first 30 minutes, compared with lispro. The half-life of both insulins also appears to be significantly shorter than that of lispro but with similar tolerability. Phase II trials are now underway.

Biosimilar insulins

As patents on existing insulins begin to expire, opportunities arise for manufacturers to produce copies of the original insulins¹⁰. It is important to remember, however, that unlike smaller molecules and chemical generics, insulin is a large and complex protein that is manufactured by biotechnology. The development of insulin biosimilars will, therefore, present a number of significant challenges, both in terms of laboratory production and regulatory review. A number of insulin biosimilars are, however, undergoing development,

including the glargine biosimilar, LY2963016 which is currently in Phase III.

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