Next step for diabetes

How faster insulin can enable the artificial pancreas

When we eat, carbohydrate in our food is broken down into glucose which is used as an energy source. Insulin is released in response to elevated levels of glucose in the blood and facilitates glucose transport to cells throughout the body.

In diabetes, on the other hand, insulin production is either insufficient (type 1 diabetes, T1D) or the action is attenuated (type 2 diabetes, T2D), causing elevated blood glucose concentrations or hyperglycaemia. For diabetics it is important to control blood glucose levels within a defined range (currently 70 to 180 mg/dL). Keeping within this range reduces long-term complications attributed to the disease, such as heart and kidney disease, strokes and nerve damage, whilst minimising the risk of blood glucose dropping too low, causing hypoglycaemia.

This can result in a broad range of symptoms, ranging from confusion and slurred speech to a potentially life-threating loss of consciousness, especially when occurring at night. The current recommendation for the time spent in the normoglycemic range (time in range, or TIR) of 70-180 mg/dL is >70% for most patients. However, despite significant advances in treatment options in recent years, less than 6% of diabetics achieve adequate glucose control.[1]

The treatment of diabetes with subcutaneous insulin presents a unique treatment paradigm in that a long duration of action is required to mimic basal levels of insulin production. But as glucose levels increase following meals, it also requires a very fast action and shorter duration. Since the first use of insulin as a therapy, researchers have attempted to modify how quickly, or slowly, injected insulin works on the body to better mimic insulin release from a healthy pancreas.

A major challenge for insulin therapy has been matching the very fast increase in blood glucose observed after mealtimes. It was not until the late 1990s when protein engineering techniques became prevalent, that faster acting meal-time insulins could be developed. Here the insulin sequence was modified, and it was discovered that certain amino acid substitutions in the beta-chain could have an impact on how quickly insulin appears in the blood stream, without changing biological activity.

Three such rapid-acting analogues are currently in use. Insulin lispro was developed by Eli Lilly and Co and first approved in the US in 1996 under the brand name Humalog. This was followed by insulin aspart which was developed by Novo Nordisk A/S and first approved in the US in 2000 under the brand name Novolog. Finally, glulysine was developed by Sanofi-Aventis and approved in 2004 as Apidra. These advances have been an overwhelming commercial success, and in 2019, the combined sales of rapid acting analogues reached approximately $6.2 billion.

However, despite the major step forward that these analogues provide, sub-cutaneous injection of rapid-acting mealtime insulin still has a significantly slower action profile than healthy pancreatic insulin release. For rapid-acting analogues, it can take between 15 and 30 minutes after injection for them to appear in the blood stream and a further 60 minutes before peak concentrations are reached. This is around 30-45 minutes slower than insulin release in non-diabetics.

Therefore, to minimise blood glucose excursions, rapid-acting insulin must be injected some 15 to 20 minutes prior to eating. The total duration of action of these analogues also struggles to match normal physiology, with a glucose lowering effect still observed four to five hours after injection. Even with pre-meal adjustments, patients risk post-meal blood glucose excursions.

Initially this can be hyperglycaemia as insulin absorption struggles to catch up. Later it can be hypoglycaemia from prolonged insulin action and 'stacking' of insulin activity. Further confounding factors such as the size of a meal, exercise and age affect the time spent in the ideal glucose range, as well as the burden on the patient to manage his/her own care.

In parallel to advances in how insulin therapy acts on the body, insulin delivery has also received great attention. As early as the 1960s the idea of continuous insulin infusion emerged in the US with the work of Arnold Kadish. It was not until 1983 however that the first body worn insulin infusion pump was licensed for commercial sale, the Nordisk Infuser.

Although a ground-breaking step, early pumps had several drawbacks. They suffered from performance and reliability problems, were large and heavy, and due to challenges with the technology, were linked to several clinical complications including hyperglycaemia, diabetic ketoacidosis, and infection at the injection site, limiting early adoption.

Today continuous insulin infusion pumps are smaller, lighter, and significantly more advanced, reducing clinical complications and improving time in range over multiple daily insulin injection regimes. Insulin pumps work by continuously infusing micro pulses of insulin through a subcutaneously inserted cannula to mimic patient specific basal levels of insulin throughout the day. Mealtime insulin requirements must be manually announced to the device, where a larger bolus dose is then infused.

Improved glycaemic control and convenience offered by pumps has fuelled adoption with one 2019 study, focused on diabetes centres in Germany and Austria concluding that pump use in type 1 diabetes had increased from 1% in 1995 to 53% in 2017.

However global adoption is lower, for example in England around 16% of people with T1D are using insulin pumps. A large body of research is currently focused on the next step for subcutaneous insulin delivery through an automated, fully closed loop pump device often referred to as the artificial pancreas.

The aim of such devices is to significantly improve TIR with the minimum possible amount of user input. Such

devices are made up of three components: the pump, a continuous interstitial glucose monitor (CGM), and a control algorithm hosted on a device such as a smart phone. The role of the control algorithm is to monitor glucose levels reported by the CGM and vary the insulin infusion rate accordingly, to maintain the user's blood glucose within appropriate limits. Fully closed loop detection and automatic dosing of insulin for mealtime glucose rises have been attempted, but glucose control is often compromised because of delays in the absorption of subcutaneous insulin. In addition, the extended duration of action for insulin can result in stacking of glucose lowering activity, further confusing the control algorithm.

The Juvenile Diabetes Research Fund estimates that the development of a fully closed loop artificial pancreas system that delivers an improvement in TIR from the current baseline of ~70% to 95% would both drive adoption of the system and have clear patient benefits which are estimated to achieve $18 billion in annual economic impact benefit in the US, with similar reductions predicted in other countries.

There is a broad consensus that to achieve such goals insulin therapies with a faster onset and duration of action, alongside technological advancements, are essential. The growing realisation of the need for even faster insulin has resulted in considerable development activity in the last 10 years, culminating in the approval of the first Ultra-Rapid Acting insulin Fiasp (Novo Nordisk) in 2018, following by Eli Lilly's Lyumjev in 2020. Both are reformulations of existing rapid-acting analogues and include additional chemical excipients that further enhance absorption, offering a faster onset of glucose lowering activity compared with Novolog and Humalog respectively.

Other ultra-rapid insulins are in development including Biochaperone Lispro (Adocia/DongBao), a reformulation of insulin lispro in late-stage development, which incorporates the company's proprietary biochaperone technology. As well as early phase development candidates such as Thermalin's T-1123 and Novo's ideal pump insulin, both are novel analogues. Once optimal speed of onset and duration of insulin action has been achieved and approved, closed loop systems have the potential to change the landscape of insulin delivery, with the potential to automatically control blood glucose.

At Arecor we have developed a proprietary formulation technology that controls chemical and physical degradation and is applicable to a wide range of therapeutics. In the case of insulin, we have employed this technology to enable a novel reformulation of insulin aspart that is both stable for use in pumps and ultra-rapid acting, called AT-247. In a single-centre, randomised double blind, three-period crossover at the Medical University of Gratz (NCT03959514) we evaluated the pharmacodynamics and pharmacokinetics of 19 adult male T1D participants in a euglycaemic clamp setting.

Each participant received a single sub-cutaneous dose of AT247, as well as a rapid-acting and ultra-rapid acting comparator. These preliminary results were encouraging and demonstrated a five-fold increase in insulin exposure and 12-fold increase in glucose lowering effect in the first 30 minutes compared to the rapid-acting comparator and a two-fold increase in insulin exposure and three-fold increase in glucose lowering compared with the ultra-rapid comparator. No safety signals were detected. Together these results demonstrate that faster acting subcutaneous insulins are achievable, paving the way for automated, closed loop systems and a potentially significant improvement in glycaemic control.

Reference:

1. International Diabetes Federation; Diabetes Atlas 9th Edition 2019, IQVIA MIDAS 2017

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