Case Insulin

by

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Introduction

***Insulin** is an example of a biopharmaceutical product used for treatment of diabetes. Insulin is a peptide hormone. There are 51 amino acids in an insulin molecule. It has a molecular mass of 5808 Da. Insulin (composed of a A-chain and a B-chain) is processed from the larger peptide proinsulin illustrated below.*

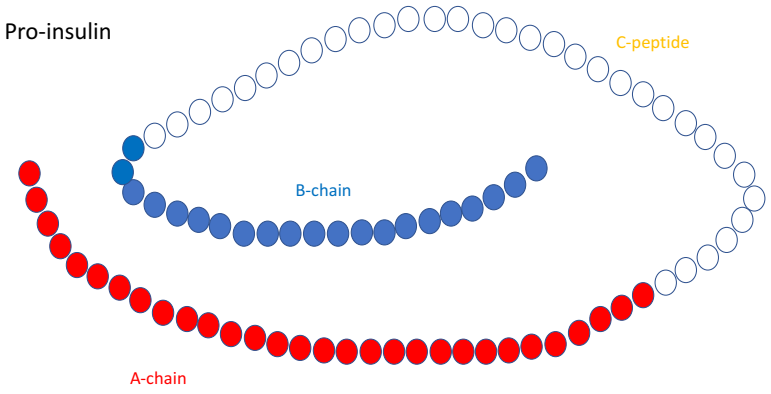

Figure: Insulin structure.

Insulin is produced in the islets of Langerhans in the pancreas. The name insulin comes from the Latin "insula" for "island" with the cells that produce the hormone in the pancreas. Insulin's structure varies slightly between species of animals. Both porcine (from pigs) and bovine (from cows) insulins are similar to human insulin, but porcine insulin resembles human insulin more closely.

Insulin is a hormone that is important for metabolism and utilization of energy from ingested nutrients – especially glucose.

Insulin is thus secreted primarily in response to elevated blood concentrations of glucose, and insulin regulates the level of blood glucose. A high glucose level is one of the major disease manifestations of diabetes, and insulin is thus essential for treatment of diabetes.

The companies Novo Nordisk A/S, Eli Lilly and Sanofi Aventis are currently the main producers of recombinant insulin.

Insulin´s commercial history.

Insulin was isolated from animal sources for the first time in 1921, and it was commercialised within 12 months. The process was therefore very different from research and development activities today. Scientists Frederick G. Banting and Charles H. Best, working in a laboratory at the University of Toronto, isolated the polypeptide hormone and began testing insulin in dogs. By 1922, with the help of James B. Collip and pharmaceutical company partners, the researchers could purify and produce animal-based insulin in larger quantities for treatment of patients with diabetes.

Insulin injections have been the standard treatment of diabetes since 1924. The innovation activities conducted in the 1920s enabled the survival of patients with diabetes. For 60 years, cattle and pigs were the sources of insulin. Although these products were highly effective, concerns arose about the growing diabetic population, long-term supply, and potential allergic reactions. insulin derived from animal pancreases had several limitations, including erratic effects on glucose levels and allergic reactions, both resulting from the production of insulin antibodies by the patient's immune system. This immunogenicity was thought to be the result of contamination of insulin with other pancreatic substances and small differences in amino acid composition between human and animal insulin. Purified animal insulins were developed and reduced the occurrence of allergic reactions, but further improvement was needed.

Scientists succeeded in synthesizing insulin in the 1960s, but synthesis was not seen as a viable commercial alternative to animal insulin.
With the new technology of genetic engineering in the 1970s, new options emerged for making synthetic insulin, that is chemically identical to human insulin. In 1978, the biotech company Genentech and City of Hope National Medical Center produced human insulin in the laboratory using recombinant DNA technology. Just four years later, in 1982, the insulin product, Humulin, became the first recombinant drug approved by the United States Food & Drug Administration. This innovation development enabled the development of a safer insulin product to patients and the development of a more cost-efficient largescale manufacturing process of insulin.

Recombinant insulin analogs

Recombinant technology for production of biopharmaceuticals came along first from Genentech and Eli Lilly in 1978, when they inserted cloned insulin genes into bacteria and created Humulin R (rapid insulin analog) in 1982. Novo Nordisk created its own recombinant insulin reaching the United States by 1988 by making a chemical conversion of bovine insulin into human insulin. Novo Nordisk has subsequently produced insulin in recombinant yeast.

Thereafter, scientists changed amino acids in insulin to create new insulin analogs with different properties. Rapid-acting insulins are typically taken at meal times. The absorption of insulin after subcutaneous injection can be improved by increasing the rate of dissociation of insulin molecules into monomers. Rapid-acting insulins are produced by engineering insulin variants with amino-acid changes that reduce the tendency of the insulin molecules to self-associate. This facilitates more rapid absorption from the subcutaneous tissue.

In 1996, lispro became the first fast-acting insulin analog to be approved, with the aim of better minimizing postprandial glucose levels. New fast-acting insulin were subsequently commercialized after lispro (aspart in 2000 and glulisine in 2004). Intermediate-acting insulins were also available. With each new, incrementally better insulin analog´s developed, new patents were issued, thus preventing generic competition.

Long-acting insulin analogs were also developed to reduce hypoglycemia and improve overall diabetes control. Glargine was the first long-acting analog commercialized on the U.S. market in 2000, followed by detemir in 2005. The first patents on these products expired in June 2014.
Long-acting insulins ensure a constant low level of plasma insulin in the fasting and interprandial state that is essential to maintain overall glycaemic control and to complement the rapid-acting insulins given at mealtime. These insulins have a longer duration of action due to slower rates of absorption from subcutaneous tissue. This is achieved by reducing solubility at physiological pH by mixing with protamine (NPH insulin) or zinc (Lente insulins), by engineering insulin variants with increased isoelectric points (insulin glargine) or by covalent acylation (insulin detemir), which promotes reversible binding with albumin to create an insulin depot.

Insulin analogue constructs

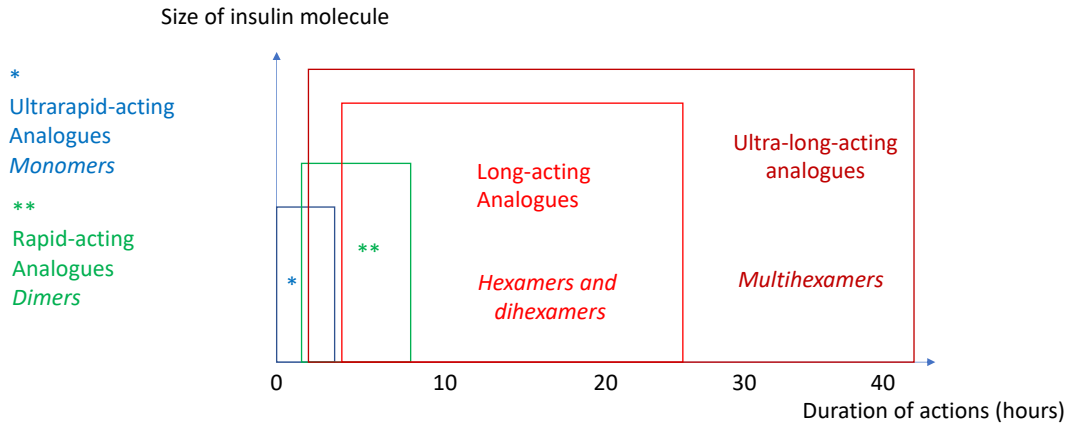

Figure: Categorisation of insulin analogues

All in all, the innovation leading to the development of new modified insulin analogs with improved pharmacokinetic properties have enabled patients with diabetes to obtain a better control of their blood glucose levels.

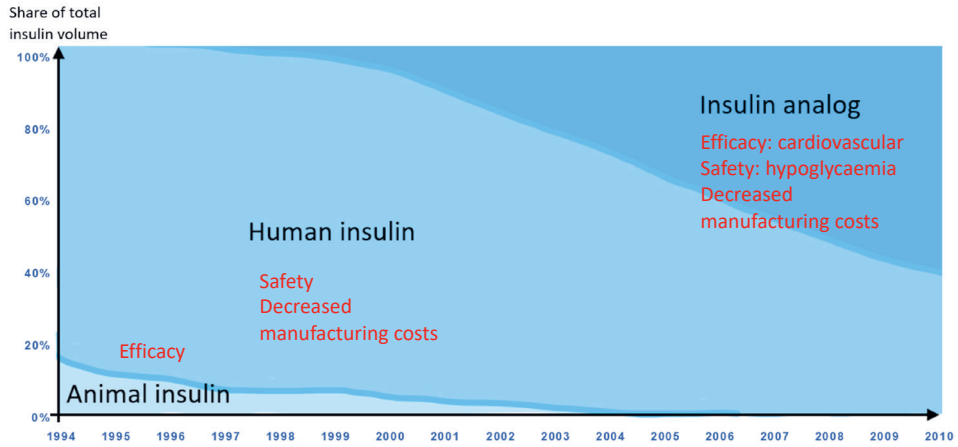

Figure: Insulin innovation replacements and their benefits

The incremental innovation by insulin analogs has until recently repeatedly precluded the formation of a generic insulin industry in North America when earlier patents expired. Thus, patent monopolies for insulin have until recently not been replaced by generic competition. The insulin analogs have been safer,

more effective, or more convenient than their predecessor. Because of that, generic drug manufacturers have not invested in producing older versions of insulin that may already be obsolete.

In addition, insulin has to be liquid. It has to be stored in heavy glass containers, preserved in cool conditions, and insulin only has a shelf life of three to six months. Shipping costs may be more than the cost to produce insulin. These entry costs may have discouraged traditional generic companies from competing in the past.

Finally, most insulin products available in 2014 were also protected by formulation or pen-device patents.

Now, with patents of the first insulin analogs expired, "biosimilars" have entered the picture. Lilly and Boehringer Ingelheim's biosimilar version of glargine was approved in the European Union in 2015. In the United States, the same product received tentative approval from the Food and Drug Administration, but final approval was being held up for 30 months, until mid-2016, because Sanofi has filed a lawsuit claiming patent infringement.

Meanwhile, unregulated biosimilar insulins have appeared in countries with less strict regulatory policies, including China, India, and Mexico.

Biosimilar insulins are not likely to produce the same cost savings as generic, small-molecule drugs, given the additional data that will be required to prove their safety and efficacy, including immunogenicity studies. Economists estimate that the price reduction for biosimilar insulins might not exceed 20% to 40%, in contrast to the 80% or greater cost savings from most other generic small molecule drugs.

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