NEWER INSULINS

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ABSTRACT
Insulin was discovered in 1921 by a surgeon, Dr. Frederick Banting, and Charles Best, a medical student after experimenting on a number of dogs in Toronto, Canada. It was possible for these two scientists to successfully demonstrate the blood lowering effect of insulin only by the assistance of John Macleod, a Professor of Physiology and Bertram Collip, a Biochemist who offered them their services and laboratory to carry out the experiments. In 1923 they were awarded the Nobel Prize for their discovery. The last one decade has seen the introduction of a variety of newer insulins prepared in different formulations by r DNA technology with distinct pharmacokinetic profiles. Consequently these newer insulins can be better accommodated in the management of diabetes mellitus and yield better blood sugar control. This would also go a long way in minimizing the complications associated with long duration diabetes mellitus.

Keywords: Lispro, aspart, glargine, inhaled insulins.

Discovery of insulin
In 1921 a surgeon, Dr. Frederick Banting, John Macleod a Professor of Physiology, Charles Best, a medical student and a biochemist Bertram Collip were successful in demonstrating the blood lowering effects of insulin on dogs. In January 1922 in Toronto, Canada, a 14-year-old boy, Leonard Thompson, was the first patient with diabetes to receive insulin and positive response with improvement in his condition was also observed. In 1923 the Nobel Committee decided to award Banting and Macleod with the Nobel Prize in Physiology or Medicine. Banting and Macleod felt that Best and Collip equally deserved the Nobel prize so they shared it with them1.

Chemistry of insulin
Insulin is a small protein with a molecular weight of 5808. It contains 51 amino acids arranged in two chains A and B linked by disulphide bridges. (Fig.1) This 3 dimensional structure of insulin is a Monomer2.
The 3 dimensional structure of insulin molecule (insulin monomer exists in 2 main conformations) differ in the number of helix in the B chain. In acid solutions the insulin molecule assembles as dimmers. (Fig-2) At neutral pH and in the presence of zinc (Zn$^{2+}$) ions it assembles as hexamers. Monomers and dimmers diffuse rapidly into blood. Hexamers diffuse poorly into blood. Insulin preparations with high hexamer proportion have a slow and delayed absorption$^{3,4,5}$.

**INSULIN RECEPTOR**

The target organs of insulin action are the liver, muscle and the adipose tissue. The insulin receptors are present in all mammalian tissues but they differ in the number of receptors. If the erythrocytes have 40 receptors on its surface the hepatocytes and adipocytes have 300,000 receptors.$^{(4)}$
EFFECT OF INSULIN ON TARGET ORGANS
It promotes storage of fat, storage of glucose, metabolic functions of a number of tissues and influences cell growth.

INSULIN PREPARATIONS
Commercial Insulin preparations differ in a number of ways. They differ in the amino acid sequence (beef, pork), difference in the recombinant DNA production techniques, - concentration, solubility, time of onset and duration of their biological action.

The principal types depending on their duration of action are the rapid acting, short acting, intermediate acting and the long acting insulins. An Inhaled form of rapid acting insulin is also marketed.

RAPID ACTING INSULIN
These insulins have a rapid onset and early peak action and the duration of action lasts for 3 to 5 hours. This permits more physiological prandial insulin replacement. There are 3 injected rapid acting analogs, insulin lispro, aspart and glulisine. An inhaled form of rapid acting insulin prepared by recombinant technology is also available.

The advantages of rapid acting insulins are that it more closely mimic normal endogenous prandial insulin secretion than regular insulin and also has an additional benefit of allowing insulin to be taken immediately before the meal without sacrificing glucose control.

LISPRO INSULIN
It is the first monomeric insulin analog to be marketed. It is prepared by recombinant DNA technology by reversing two amino acids near the carboxyl (COOH) terminal of the B chain. The proline at B 28 is interchanged with lysine at B 29. (Fig. 3)

![Diagram of Human Insulin and Lispro Insulin](image)

Lispro insulin is stabilized into hexamers in vials by a cresol preservative to enhance the shelf life. When injected subcutaneously it quickly dissociates into monomers and is rapidly absorbed. The onset of action starts within 5 to 15 minutes and peak activity is at one hour. The time of peak action is relatively constant regardless of the dose.

The therapeutic advantages of lispro over human insulin are decreased prevalence of hypoglycemia to an extent of 20-30% and improved glucose control as assessed by HbA1c (0.3% - 0.5%).

INSULIN ASPART
It is produced by the substitution of proline at B28 with a negatively charged aspartic acid. This modification decreases monomer-monomer interaction between normal proline at B28 and glycine at B23 thereby inhibiting insulin self aggregation. It dissociates rapidly into monomers. Its absorption and activity profile is similar to that of lispro insulin and plasma insulin profiles are similar with both. Glucose control and hypoglycemic effect is similar with both insulins.

INSULIN GLULISINE
It is formulated by substituting an asparagine for lysine at B3 and glutamic acid for lysine at B29. Its absorption and action profile are similar to lispro and aspart insulin.

INSULIN INHALED RECOMBINANT HUMAN
It is a powder form of r DNA human insulin that is administered through an inhaler device. It is marketed for preprandial and blood sugar control.
correction use in adults with type 1 and 2 diabetes mellitus. It is not approved for use in children, teenagers or adults with asthma, bronchitis, emphysema, smokers, within 6 months of quitting smoking. This route of administration is well tolerated. Studies have shown that less than 30% of users achieved target blood glucose after 6 months of therapy with inhaled insulins.

**SHORT ACTING INSULINS**

**HUMAN INSULIN (Regular, Soluble)**

It is short acting soluble crystalline zinc insulin prepared by recombinant DNA technology. The molecule is identical to human endogenous insulin. Its action appears within 30 minutes, peaks at 2 to 3 hours and lasts for 5 to 8 hours.

In high concentration in the vials regular insulin molecules self aggregate in anti-parallel fashion to form dimmers. These dimmers stabilize around zinc ions to create hexamers. The hexameric nature of regular insulin causes a delayed onset and prolongs the time of peak action.

The hexamers break down into dimmers and monomers as the insulin depot gets diluted by interstitial fluid and the concentration begins to fall. As with all older insulin formulations duration of action, time of onset and intensity of peak action increases with the size of the dose.

**INTERMEDIATE AND LONG ACTING INSULINS**

Neutral Protamine Hagedorn (NPH) or Isophane Insulin

It is an intermediate acting insulin. The absorption and onset of action are delayed by combining appropriate amounts of insulin and protamine so that neither is present in uncomplexed form. When given subcutaneously proteolytic enzymes degrade protamine to permit absorption of insulin. The onset of action of NPH insulin is 2 to 5 hours and the duration of action lasts for 4 to 12 hours. It is given 2 to 4 times daily for insulin replacement.

**ULTRALENTE INSULIN**

(Extended insulin zinc suspension and Protamine zinc insulin suspension)

They are long acting insulins. They have a slow onset and a prolonged peak of action. They provide a low basal concentration of insulin through the day. The long half life of ultralente insulin makes it difficult to determine the optimal dosage. Doses are given once or twice daily and the doses are adjusted according to fasting blood glucose.

**INSULIN GLARGINE**

This insulin was designed to provide reproducible, convenient, background insulin replacement. This analog is created by attaching 2 arginine molecules to the carboxyl (COOH) terminal of the B chain. In addition asparagine is substituted for glycine at A21 position.

It is a soluble peakless insulin which has a broad plasma concentration plateau and is an ultra long acting insulin analog. It is soluble at an acidic solution but precipitates in the more neutral body pH after subcutaneous injection. It may be administered at any time during the day with equivalent efficacy and no difference in hypoglycemic episodes. It results in less hypoglycemia and provides a better once daily 24 hour insulin coverage than ultralente or NPH insulin. The duration of action remains at 24 hrs. It can be combined with oral hypoglycemic drugs.

**INSULIN DETEMIR**

This insulin is the most recently introduced long acting insulin analog. The terminal threonine is removed from the B30 position and myristic acid (a C14 fatty acid) is attached to the terminal B29 lysine. This prolongs the availability of the injected insulin by increasing both self aggregation in subcutaneous tissue and reversible albumin binding. Insulin detemir has the most reproducible effect of the intermediate and long acting insulins. It is associated with less hypoglycemia than NPH insulin. It has a dose dependent onset of action of 1to 2 hours and the duration of action lasts more than 24 hrs. It is given twice daily to obtain a smooth background insulin level6.

**INHALED INSULINS**

The FDA has approved an inhaled insulin preparation of finely powdered and aerosolized human insulin. Insulin is readily absorbed into the blood stream through alveolar walls. Insulin delivered by inhalations has a rapid onset of action, peak insulin levels are achieved within 30 minutes and duration of action is 6 to 8 hours. Inhaled insulins can be used to cover mealtime insulin requirements or to correct high glucose levels. It cannot provide basal or background insulin coverage. Less than 10% of inhaled insulin dose is absorbed. Safety concerns include pulmonary fibrosis or hypertension, decreased lung volume or oxygen diffusion capacity and excessive insulin antibody formation6.

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