Insulin analogues
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Introduction
Diabetes mellitus is a very big challenge for our medical science. To overcome this problem we need newer generation of agents those can control glycaemic status nearer to physiology. In that case Insulin analogues will be the agents for improving glycaemic control.

The diabetic control and complication trail provided conclusive evidence that strict glycaemic control, reduced the incidence and progression of neuropathy, nephropathy and retinopathy.

The key to strict glycaemic control by the exogenous insulin lies in the delivery method that emulate physiological insulin secretion. Unfortunately conventional insulin preparation has limited pharmacokinetic profiles which make the goal of emulation impossible. On the other hand insulin analogues offer expanded pharmacokinetic profiles and the possibilities of regimens that closely mimic the physiology.

Insulin analogues
Analogues are altered molecular version of a natural substance. They have been used in many therapies where hormone treatment is needed. The natural hormone is changed slightly, by rearranging the position of amino acid within the molecule (i.e.- It is something like changing the position of beads on a necklace). This new version of natural substance works basically the same way as original substance.

As there is slight difference of amino acid sequences between natural human insulin and insulin analogues, it would not be correct term to call the insulin analogue a type of human insulin. So, insulin analogue and insulin are two different terms.

Historical achievement in insulin therapy
*1920- Discovery of insulin by Banting and Best.
*1922- The 14 year-old Leonard Thomson became the 1st patient to receive insulin.
*1923- Nobel prize in medicine was awarded to Banting and John McLeod.
*1930- Long acting protamine zinc insulin was developed.
*1950- Long acting insulin NPH was developed and insulin zinc (Lente) were introduced.
*1980- Development of pork insulin.
*1984- Improvement in insulin delivery device and introduction of insulin delivery pen.
*1996- In July 1996 first recombinant DNA human insulin analogue, Lispro was approved.
*1999- Insulin analogue Aspart was introduced into market.

Since then more insulin analogues have been introduced which provides new hope for controlling diabetic complications.

Normal insulin secretion
In non diabetic persons insulin secretion has two basic components-
1) Basal &
2) Stimulated.

1) Basal
   - Basal insulin is secreted continuously between meals and throughout the night at a rate of 0.5-1 u/h in adults
Basal insulin provides serum concentration of 5-15 microunit/ml. The low basal insulin reduces hepatic glucose production but allows sufficient glucose level for cerebral energy production. In diabetic patients treatment with intermediate acting and long acting insulin attempts to mimic the basal secretion.

2) Stimulated
- Stimulated secretion occurs normally in response to a meal resulting serum concentration of insulin 60 - 80 microunit/ml from just before to 30 minutes after meal.
- Concentration returns to normal level in 2-4 hours.

![Figure 1: Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.](image)

Indications of insulin therapy
1) Type-I DM.
2) Type-II DM with following conditions-
   i) Hyperglycemia despite of maximum dose of oral hypoglycemic agents.
   ii) Decompensation due to intercurrent events like infection, acute injury, stress.
   iii) Pregnancy.
   iv) Renal diseases.
   v) Surgery.
   vi) Severe hyperglycemia with or without ketonaemia or ketonuria.

Therapeutic objectives of insulin therapy
- Correction of fasting and pre-prandial hyperglycemia (correcting the basal glucose metabolism).
- Minimization of the excessive post-prandial hyperglycemia.
- Prevention of hyperglycemia in between meals.
- To keep the Hb1c near normal.

Disadvantages of conventional insulin therapy
1) Disadvantages of regular/soluble insulin
   - Regular insulin has a nature of self association and regular insulin is found in a self associated hexameric form.
   - To be absorbed by the capillary the hexameric form must dissociate to dimer and then monomer.
   - This dissociation process delays the onset of action from 0.5-1 hr, may not be peak for 4 hrs and duration of action of 8 hrs.
   - So they should be taken 30 min before meal.
   - As their duration of action is prolonged, it reaches peak concentration 2 hrs after injection (in many cases and depending on the dose it may peak 4-6 hrs after injection) when blood glucose level already may be low.

2) Disadvantages of intermediate acting insulin (NPH & Lente)
   - Peak action is 4-10 hrs after injection.
   - Effective duration of action 10-20 hrs.
   - Their peak effect is a problem for using as a basal insulin.
   - Their duration of action necessitates more than one daily injection.

3) Disadvantages of long acting insulin (Ultralente)
   - Their duration of action is 16-20 hrs. So single injection is not enough.
   - Their duration of action is variable.
   - Their peak effect is difficult to predict.
Pharmacokinetic actions of conventional Insulin at a glance

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action</th>
<th>Peak action</th>
<th>Effect of duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>0.5-1 hr</td>
<td>2-4 hrs</td>
<td>3-8 hrs</td>
</tr>
<tr>
<td>NPH</td>
<td>2-4 hrs</td>
<td>4-10 hrs</td>
<td>10-20 hrs</td>
</tr>
<tr>
<td>Lente</td>
<td>3-4 hrs</td>
<td>4-8 hrs</td>
<td>10-20 hrs</td>
</tr>
<tr>
<td>Ultralente</td>
<td>6-10 hrs</td>
<td>Dose dependent</td>
<td>16-20 hrs</td>
</tr>
</tbody>
</table>

Types of insulin analogues
1. Rapid Acting
   i) Lispro
   ii) Aspart
   iii) Glulisine
2. Long acting
   i) Glargine
   ii) Detemir

Criteria for good rapid acting analogues
- The short acting analogues would have time action profile with an onset of action less than 30 mins.
- A duration of action less than 4 hrs.
- Similar effect in all patients.
- They should be non immunogenic.

Lispro
**Structure:** Insulin Lispro was formulated on the premise that insulin like growth factor-1 (IGF-1) which structurally similar to insulin, does not trend to self associate.

In the B chain of natural human insulin, Lysine lies in the B29 position and Proline in the B28 position. Lispro is produced by inverting position of two amino acids. That is in Lispro B chain, Lysine lays in B28 position & Proline lies in 29 positions.

Lispro is non-immunogenic (In different studies it was observed that even before exposure to Lispro there is cross reactive antibodies but not Lispro specific antibody level. These antibodies decrease over time and have no clinical consequence).

Special considerations in using insulin lispro

<table>
<thead>
<tr>
<th>Potential problems</th>
<th>Comments and possible solutions</th>
</tr>
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<tbody>
<tr>
<td>Patient eats dinner late</td>
<td>Because of insulin lispro's shorter duration of action, hyperglycemia may occur because the time from lunch to dinner may be too long. Consider adding a small dose of intermediate-acting (NPH) insulin at lunch to meet basal insulin requirements between meals.</td>
</tr>
</tbody>
</table>
Patient has snacks containing more than 5 g of carbohydrate

Consider adding an additional dose of insulin lispro; if the patient also eats dinner late in the evening, this additional dose of insulin lispro can replace lunchtime basal NPH insulin supplementation.

Patient is a slow eater or a grazer (i.e., eats small amounts of carbohydrates throughout the day rather than at three meals)

Because of the rapid onset of insulin lispro, this type of patient may not respond as well to insulin lispro as to regular human insulin.

Patient has unpredictable eating habits

Insulin lispro offers the patient flexibility, in that the administration of this insulin can be timed with meals.

Patient has type 2 diabetes and is receiving two injections of NPH/regular insulin each day

This patient could benefit from the substitution of insulin lispro for regular human insulin to decrease postprandial blood glucose excursions.

Patient exercises

The patient who uses insulin lispro can expect fewer episodes of hypoglycemia if the exercise is undertaken 2.0 to 2.5 hours after the injection of insulin lispro.

Near-normal glycemic control is necessary to prevent or delay the onset of complications in patients with type 1 or type 2 diabetes. Patients with type 2 diabetes who have not responded to oral glucose-lowering agents often require insulin therapy to achieve the glycemic goals set forth by the American Diabetes Association. One study in both type 1 and type 2 diabetics concluded that insulin lispro improves postprandial glycemic control without increasing the risk of hypoglycemia. Short- or long-term insulin therapy has been shown to be useful in type 2 diabetics in whom the rapid component of endogenous insulin secretion is missing. In these patients, insulin lispro is a physiologic therapy. Primary care physicians should consider including mealtime insulin lispro in insulin regimens. The disadvantages of insulin lispro therapy are the increased risk of hypoglycemia if meal ingestion or absorption (gastroparesis) is delayed and the increased overall cost of therapy. Nonetheless, a short-acting insulin analog such as insulin lispro should provide increased convenience and flexibility to patients who are currently receiving regular human insulin. Furthermore, the characteristics of insulin lispro may help patients achieve improved long-term glycemic control and may reduce the incidence of hypoglycemic episodes. Insulin analogs may be an important tool for helping patients with diabetes mellitus achieve their target glucose goals.

**Drug Interactions**

No studies have specifically evaluated drug interactions in diabetic patients who are receiving lispro insulin. Close monitoring of blood glucose levels is important when a drug regimen is changed in any patient with diabetes.

**Aspart**

**Structure:** In insulin aspart, proline is replaced by aspartic acid at position B28 in insulin molecule.

### Therapeutic role of lispro

Insulin lispro has been found to be a safe and effective treatment for diabetes mellitus. Improvement in glycemic control is demonstrated by a decreased postprandial blood glucose concentration, although the long-term clinical significance of this improvement is as yet unknown. Multinational clinical trials have shown no statistically significant difference between hemoglobin A1c levels in patients treated with insulin lispro and patients treated with regular human insulin. However, the use of insulin lispro in external insulin infusion pumps has been shown to produce a small, yet clinically significant (0.34 percent) reduction in hemoglobin A1c levels compared with the reduction achieved using regular human insulin. This improvement in hemoglobin A1c represents an approximately 20 percent reduction in the risk of retinopathy in patients with diabetes.
This change results in stay Aspart in monomeric form and thus helps in rapid absorption.

Figure 5: Structure of lispro, aspart, glargine

**Practical issue:** Onset of action within 30 min, peak action 30-60 min and action lasts for 4 hrs.

Although some preliminary comparisons of Aspart with Lispro have suggested that they are similar in action, other comparison suggested that there are some differences. So it is not recommended that Aspart and Lispro are interchangeable.

**Glulisine**

**Structure:** Glulisine differs from human insulin in that the amino acid Asparagine at B3 position is replaced by Lysine and Lysine is replaced by Glutamic acid. It is still in clinical trial.

**Benefit of short acting analogues**

- As their onset of action very rapid, they can be used just before and even after meal.
- As their duration of action is short, they are less likely to cause hypoglycemia in between meals. This is the key point of strict glycaemic control. They rapidly reduces the blood glucose level just after meal but are not cause hypoglycemia 4-6 hrs after meal.

- So, they can be used to those who wants more flexibilities in their meal times and those who suffers late midnight hypoglycemia.
- They improve HbA1c.

**Premixed insulin analogues**

Two premixed insulin analogue preparations are now available
1) 75% Neutral Protamin Lispro + 25% Lispro
2) 70% Protamin Crystalline Aspart + 30% Aspart

**Basal/long acting insulin analogues**

Criteria for long acting insulin analogues
1) An ideal insulin analogue should have peak less effect.
2) Should have long half life, so that one injection is enough.
3) Little inter-patient and intra-patient variability.

**Basal & long acting insulin analogues**

Two long acting analogues are available
1) Glargine
2) Detemir

**Glargine**

**Structure:** Glargine is produced by recombinant DNA technology through nonpathogenic E. Coli. The difference is only in structure from human insulin where Glargine has both the addition of two Arginine at C-terminus of B-chain and substitute of Glycine for Aspargenic acid at A21 position.

**Practical issue:** This change in structure makes Glargine soluble in pH of 4 but has relatively slow solubility when injected into neutral pH environment.

When Glargine is injected, micro precipitates forms and slowly insulin resolubilized and absorbed. This sequence of changes is predictable and provides a relatively constant level of insulin with no peak effect over a period of 24 hrs. So, single injection can maintain constant level for 24 hrs.
There is no difference in absorption rate of Glargine in different sites of the body. There is no evidence that Glargine accumulates in the body. Large number of trials have documented that Glargine can control glycaemic status more strictly then NPH, Lente or Ultralente but significantly reduces the nocturnal hypoglycemia. It significantly reduces HbA1c than other intermediate & long acting insulin.

Detemir

It is under trial.
- After injection, Detemir binds with the albumin through a fatty acid chain attached to Lysine at residue B29, which leads to a reduction in free Detemir level.
- The initial data suggested that Detemir has less variability in absorption than NPH.
- Data suggested it is less hypoglycemic.
- One study suggested that Detemir has some effect on hepatic glucose metabolism.

Limitations of insulin analogues
- May cause hypoglycemia on overdose or if patient don't take adequate amount of food prior to injection.
- Insulin analogues are not recommended for I.V use.
- Rapid acting analogues are not recommended in diabetic gastroparesis.
- Insulin allergy, lipoatrophy and lipohypertrophy same as conventional insulin.
- Glargin requires OHA in Type-II & regular insulin in Type-I DM.

Conclusion

Insulin treatment has always been as much an art as a science. Insulin analogues have met all the requirement for strict glycemic control also give the patient more flexibility in the timing of meal without the risk of hypoglycemia. Although these insulin analogues have much benefit over conventional insulin, the cost of these analogues is the main disadvantage for their use.

Reference