



Newer Insulins

Jasleen Kaur, Dinesh K. Badyal

Introduction

Diabetes is rapidly reaching epidemic proportions, affecting 174 million people worldwide and this number is likely to double by year 2030 (1). Insulins are the mainstay of treatment in type I diabetes and also in later stages of type II diabetes. Left uncontrolled diabetes can lead to coronary heart disease, kidney failure, blindness, limb amputation and premature death. Therefore, compliance with the insulin therapy is important in preventing the adverse clinical effects of the disease. Insulin treatment in type 1 and type 2 diabetes has come a long way since its discovery by Banting and Best in 1922. In 1980s with the help of recombinant DNA technology, human insulins were discovered which replaced animal insulins. Human insulins have reduced the adverse effects of animal insulins such as insulin allergy, insulin resistance and insulin lipodisatropy (2).

Problems with Conventional Insulins

Initial modifications of insulin structure produced insulins with varying pharmacokinetics, but not mimicking the physiological insulin released. Normally, insulin concentration peaks at 30-45 minutes after a meal and returns to basal level after 2-3 hrs. The onset of action of regular insulin is too slow, its action peaks at 1-2 hrs after an injection and the duration of action is too long i.e. 6 hrs to mimic the physiological insulin pattern. This leads to post prandial hyperglycemia and late hypoglycemia. It is therefore, recommended to administer regular human insulin 30-45 minutes before meals, which restricted patient lifestyle and compliance (3). Similarly the available intermediate or long acting insulin preparation are unable to provide continuous basal insulin for 24 hrs. This caused premeal and fasting hyperglycaemia and night hypoglycaemia (4). Moreover, conventional human and porcine insulins tend to form hexamer in contact with

zinc in the bloodstream. Insulin in the form of hexamer will not bind to its receptors because, hexamer has to slowly equilibrate back into monomers to be clinically useful (5).

Newer Insulins: Novel long and short acting insulin analogues, the so-called 'designer insulins', developed through genetic engineering in the 1990s, paved the way for more physiological insulin therapy. They were theoretically less problematic in terms of hypoglycemia and patient satisfaction. They made the treatment flexible, safer and simpler. Newer Insulins are faster acting preprandial insulin or longer acting basal insulin which provide a constant concentration with no peak increase in insulin level. Newer analogues exist as monomers and are absorbed much faster (insulin aspart or lispro) or absorbed very slowly (insulin glargine or detemir). The newer analogues have increased stability, less variability and selective action which will help in developing individualized treatment suitable to specific patient characteristics and will improve glycaemic control. Structure function studies have shown that amino acid essential for binding the insulin receptor include A 1-3,19, B-6,12,23-25. The B 26-30 region is critical for insulin receptor recognition and has been the site preferred for structural alteration with the aim to modify the pharmacokinetic profile of insulin molecule (6). It is also important in mediating the formation of dimers.

Table-1 Advantages of Insulin Analogues

1. They provide better control of sugars
2. They carry low risk of hypoglycemia particularly nocturnal hypoglycemia
3. They do not have to be injected half an hour before meals
4. Compliance is improved with long acting analogues as once a day the insulin
5. The need for snacks between meal may be reduced with short acting analogues
6. Advantage in term of weight gain epically with detemir insulin.

From the Department of Pharmacology, Christian Medical College and Hospital, Ludhiana, 141008, India.

Correspondence to : Dr. Dinesh.K. Badyal, Head, Department of Pharmacology CMC, Ludhiana India.



Major concern of all insulin analogues is their altered mitogenic properties and risk of carcinogenicity on long term.

A. Short-Acting Analogues

These have rapid onset and shorter duration of action. The peak of onset corresponds more closely with the post prandial glucose peak. Therefore, can be administered immediately before meals (7,8). This avoids post prandial hypoglycaemia that occurs due to long duration of action of soluble insulin (9). The shorter duration of action of these analogues leads to lower incidence of hypoglycaemia. The agents are:

i) Insulin Lispro

It was the first recommended DNA analogue, approved by FDA in 1996. It was developed with the aim of improving glycaemic control at meal times. There is inversion of proline at position 28 with lysine at position 29. This modification did not alter receptor binding, but blocked the formation of insulin dimer and hexamer. This allowed larger amount of active monomeric insulin to be available for postprandial or after meal, injections. It also acts rapidly, so it can be injected 15 minutes after meals in patients with type I diabetes without compromising blood glucose control. The studies with insulin lispro found that in comparison to soluble insulin the post prandial rise in serum glucose was lower, glycosylated hemoglobin level was also lower and hypoglycaemia was also less (10). But the treatment satisfaction and treatment flexibility scores were higher with insulin lispro. Insulin lispro has been tested for use in pregnancy and gestational diabetes. It was found to be as effective as regular insulin and no teratogenic effects were noted.

ii) Insulin Aspart

It was created by recombinant DNA technology by substitution of proline at 28 position with aspartic acid. This analogue also prevents the formation of hexamers leading to rapid absorption from subcutaneous tissue than soluble insulin (11). It has short duration of action. Glycaemic control was better as measured by decrease in post prandial blood glucose level and glycosylated Hb level as compared to human soluble insulin (12). It has similar binding properties and mitogenicity characteristics

as regular human insulin and has equivalent immunogenicity.

iii) Insulin Glulisine

It differs from human insulin by substitution of asparagine at position B3 by lysine and lysine at position B 29 by glutamine. It has rapid onset and short duration of action than regular human insulin. It exerts its action by causing insulin receptor substrate-2 (IRS-2) phosphorylation and also has antiapoptotic activity against cytokine and fatty acid induced β -cell destruction (13). Due to antiapoptotic activity, it counteracts autoimmune and lipotoxicity induced β -cell destruction. It has advantage over regular human insulin by causing less chance of hypoglycemia by administering just before meals. But insulin glulisine carry the risk of tumorigenicity (14) as various studies have shown that by substitution at position B28-30 causes increased binding to IGF-1 receptor and increases mitogenic activity (6).

B. Long Acting Analogue

Ideal basal insulin has long duration of action and provide 24 hour control with minimum variation in absorption and has to be given once a day. Traditional intermediate and long acting analogues i.e. isophane, lente and ultralente are unsatisfactory. Isophane insulin has peak onset 4-6 hrs after injection followed by waning of activity therefore, if given at bed time, insulin level peaks at 12-2.00 am when less insulin is required and causes nocturnal hypoglycemia (4). Further duration of action of isophane insulin is not long enough to cover the insulin requirement till dawn. Ultralente insulin has long duration of action (12-28hrs) but high degree of variability among patient is seen after subcutaneous injection. Accumulation leads to a steady state after several days of treatment, which prevents flexible dose adjustment according to patient's needs (15). Two long acting insulin analogues have been developed, insulin glargine and insulin detemir. They have made significant improvements in the management of type 1 diabetes both in terms of improvement in glycaemic control and in reducing hypoglycaemia rates (16). They were developed on two approaches:- Changing the insulin pH to neutral, causes



Table:1 Newer Insulins

Insulins	Date of Approval	Indication
1. Short Acting <i>Insulin lispro</i> (Humalog) <i>Insulin aspart</i> (Novolog) <i>Insulin glulisine</i> (Apidra)	June 14, 1996 June 07, 2000 April 26, 2004	In type I and type II diabetes mellitus along with long acting insulin In Type I and II adult DM along long acting insulin & in insulin pumps In Type I and II adult DM and in insulin pumps
2. Long Acting <i>Insulin glargine</i> (Lantus) <i>Insulin detemir</i> (Levemir)	April 20, 2000 June 16, 2005	In Type I and II DM In Type I Type I DM as add onto long acting Type II DM alone or along with oral antidiabetics or long acting insulin
3.. Inhaled Insulin (Exubera)	June 27, 2007	

it to precipitate in the subcutaneous tissue, therefore delaying its absorption. -Binding insulin to serum carrier with prolonged half life delays its absorption.

i) *Insulin Glargine*

It was the first long acting basal human insulin available in the market. It was created by modifying three amino acids, with the aim to have long duration of action and no pronounced peak activity. The structure was designed by substituting an asparagine residue with a glycine at position 21 of the A-chain and elongating the B-chain at the C-terminus by addition of 2 arginine residues (17). Modification of B-chain caused the pH to shift from 5.4 to 6.7 and makes it less soluble at physiological pH and more soluble at acidic pH. The glycine substitution of A chain of insulin glargine stabilizes the hexamer structure and therefore, contributing to delayed delivery from subcutaneous depot and maintaining its stability in acidic solution. Insulin glargine is not to be mixed with other insulin, as it becomes cloudy and results in alteration of pharmacokinetic and pharmacodynamics profile. It precipitates at physiological pH and absorbs slowly from injection site. Therefore, provides basal insulin that mimic insulin profile of healthy individual (18). It has slow onset of action and achieves a maximum effect after 4-6 hrs and this activity is maintained for 11-24 hours or longer. The studies with insulin glargine found that fasting blood glucose were lower, nocturnal hypoglycaemia was less and patient had greater treatment satisfaction in comparison to isophane insulin in type I and II diabetes mellitus (19,20). Injection site pain is more in patients with insulin glargine than isophane insulin. Insulin glargine has more affinity to the insulin growth factor 1 receptor (IGF-1), therefore has increased mitogenic potency compared

to human insulin in in-vitro studies (6). But clinical significance of this is not very clear. Patients with type 2 diabetes mellitus on insulin glargine had increased progression of retinopathy, but this risk is also not very clear (21).

ii) *Insulin Detemir*

Modifying insulin by binding to serum protein albumin prolongs the duration of action (22). It is a soluble basal insulin analogue at neutral pH. It is created in which amino acid threonine at B 30 is removed and acetylated with a 14-C fatty acid chain to lysine B29. which causes it to bind reversibly to albumin in plasma. Only free insulin detemir is biologically active and its slow dissociation from albumin results in delayed action. Its onset of action takes 1-2 hours and duration of action is for 24 hours. It is given twice daily to obtain a smooth basal insulin level. It is shown to be as effective as other long acting analogues i.e. isophane insulin (NPH) in maintaining glycemic control in high doses and fewer episodes of hypoglycemia (23). Reduction in body weight is another advantage which may be due to direct effect on hypothalamus (24). But its lower affinity for insulin receptor necessitates higher doses compared to human insulin. In another study where insulin detemir was compared with insulin glargine and found that the time-action profiles and the duration of action were comparable but within-subject variability in the metabolic effect was significantly lower. Therefore, insulin detemir seem to be as well suited as insulin glargine for once-daily administration in type 2 diabetes (25). It has low insulin receptor binding affinity and metabolic potency. It is less potent in binding to IGF-1R & stimulating mitogenesis. Therefore, it has reduced risk of inducing tumours (6).



C. Other newer insulins

i) *Albulin*

It is the newest insulin analogues which is developed and reported by Duttaroy et al, in 2005 (26). It is a single chain analogue produced in yeast or mammalian cell. It consists of B and A chain of human chain linked by a dodecapeptide linker and fused to NH(2) terminal of native human serum albumin. It has been shown in various studies that it has lower affinity to bind to insulin receptors (26). Albulin displays characteristics of a potent long-acting insulin analog that can be evaluated for use as a novel insulin therapy for patients with insulin-dependent diabetes.

ii) *Inhaled Insulin*

By pulmonary route drugs have faster onset of action, even faster than i.v. route and large surface area of lungs causes more systemic absorption (27). If long-term safety and efficacy is confirmed, inhalation will become the first non-subcutaneous route of insulin administration for widespread clinical use. Exubera is first inhalational drug to be approved by FDA on Jan 2006. Exubera is an insulin product for pulmonary delivery in powder form. Bioavailability is just 10% compared to regular human insulin given by subcutaneous route with duration of action of 5-10 hours (27). Therefore, high doses of insulin have to be given about 8 times the subcutaneous route to achieve glycemic control. The major problems are loss of drug with inhaler and mouth during inhalation, variation in absorption due to age related difference, respiratory tract infection and smoking. Other side effects are mild to moderate cough, shortness of breath, sore throat and dry mouth.

iii) *Other Routes*

Despite overwhelming interest and investment in administering insulin via the oral route, success is not expected in the short term. Administration of insulin through buccal mucosa and skin are also continuing. Pancreatic transplantation has also been tried but this will remain limited to those patients receiving a kidney transplant and immunotherapy. Islet cell transplantation

is at an early though encouraging stage following the availability of new less toxic immunosuppressive agents (28).

Conclusion

These analogues have shown equal or superior efficacy and have lower incidence of hypoglycaemia. But insulin analogues are more expensive than human insulin. Therefore, these are used as alternative agents in patients who cannot achieve tight blood glucose control, patients with hypoglycaemia or intolerable events with human insulin and in patients who have to start human insulin therapy. The proper use of insulin analogues will allow the diabetics greater flexibility in the timing of meals, snacks and exercise which will improve their quality of life. Other routes of insulin administration are also showing promise. Inhaled insulin has been approved by FDA. Continued progress in the field of newer insulins is on as well.

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