

Modern Insulins — The Insulin Analogues: A Reappraisal

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HISTORICAL PERSPECTIVE

Since the extraction and introduction of insulin by Banting, Best, Macleod and Collip in the 1920s, several modifications have been made in the provision of subcutaneously administered insulins. The short glucose lowering effect of raw insulin was found to result in insufficient glycaemic control. The first modifications of insulin sought to prolong action by adding protamine and excess zinc and this resulted in the introduction of Protamine zinc insulin in 1936¹ and NPH insulin in 1946².

Highly purified monocomponent insulins were developed in the 1970s, with the availability of modern purification techniques. The establishment of recombinant DNA technology enabled the production of recombinant human insulin by the 1980s.

However, standard insulin based regimens poorly recreate the physiological action profile of endogenous insulin. The limiting pharmacokinetic and pharmacodynamic features of standard insulins, which frequently lead to hypoglycemia as one tries to achieve ideal glycaemic control lead to a renewed interest in producing safer insulin formulations that closely duplicate endogenous insulin secretion. This interest has led to the development of insulin analogues that are characterized by flexible, predictable and physiological action profiles along with freedom from the fear of hypoglycemia.

INTRODUCTION

The advent of recombinant DNA technology in the 1980, allowed the synthesis of insulin analogues, which gave people with diabetes a great degree of treatment flexibility.

Insulin has a natural tendency to associate into dimers and hexamers at high concentrations and neutral pH. Altering the amino acid sequence of insulin to prevent self association such as those that promote charge repulsion and hydrophobicity repulsion results in insulin with a faster onset and shorter duration of action. These insulins exist as monomers and are absorbed two to three times faster than regular insulin and are termed rapid acting insulin analogues.

On the contrary, changing the amino acid sequence to make insulin less soluble at physiological pH can delay its absorption and can result in long acting analogues.

TYPES OF INSULIN ANALOGUES

Insulin analogues are classified as

- a. Short acting analogues –Insulin lispro, Insulin aspart
- b. Long acting analogues –Insulin glargine, insulin detemir
- c. Premix analogues.

Short Acting Analogues

They were developed as an alternative to soluble insulin. The peak of action corresponds closely to the post prandial glucose peak and hence can be injected immediately before meals as compared to 30-45 minutes before for soluble insulin. This property translates into more treatment flexibility and avoidance of postprandial hypoglycemia.

1. Insulin Lispro

Insulin lispro (Humalog) was developed with the aim of controlling post prandial glycaemic excursions.

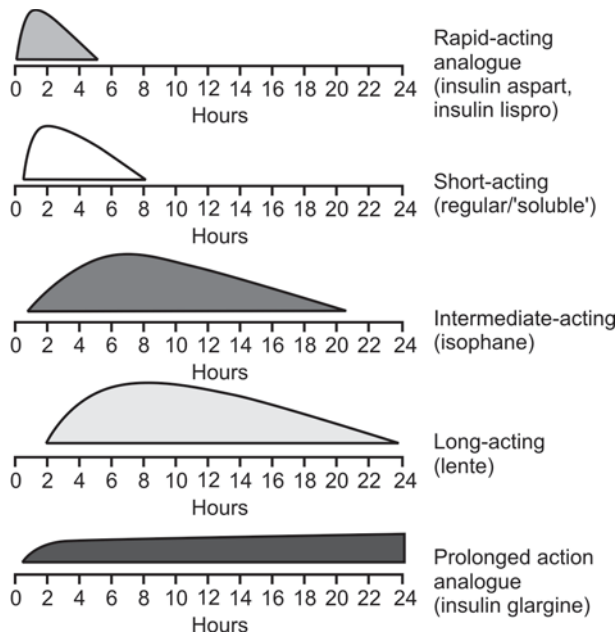


Fig. 1: Onset and duration of action of insulin preparations

The inversion of proline (position 28) and lysine (position 29) residues results in rapid dissociation of insulin hexamers into monomers resulting in a faster absorption profile³. Onset of action is about 15 minutes and duration of action 2-3 hours and it should be administered subcutaneously 15 minutes before or immediately after a meal.

Trials

In studies of people with type 1 DM, the postprandial glucose levels were much lower with insulin lispro administered before meals, when compared to soluble insulin given 30-40 minutes before meals. HbA_{1c} levels were also lower in those treated with insulin lispro. In addition, the rate of hypoglycemia was 12% lower in the insulin lispro treated group (6.4 ± 0.2 vs 7.2 ± 0.3 episodes/ 30 days)⁴.

In people with type 2 DM, the rise in postprandial glucose levels after insulin lispro was 30% lower at 1 hour and 53% lower at 2 hours when compared to human soluble insulin. The number of hypoglycemic episodes also showed a significant reduction⁵.

2. *Insulin Aspart*

Insulin aspart (novorapid) differs from soluble insulin by the replacement of proline at position B28 with aspartic acid. This results in faster dissociation of hexamers into monomers and dimers thus resulting in a faster absorption profile. Insulin aspart has an onset

of action of 10-20 minutes, reached maximum serum concentration at 45 minutes and has a duration of action between 1-3 hours.

Trials

In a six months study in 822 type 1 diabetics treatment with insulin aspart was associated with better glycemic control as evidenced by lower postprandial and HbA_{1c} levels when compared to soluble insulin. This benefit was accompanied by fewer hypoglycemic events⁶.

A comparative study of insulin lispro and insulin aspart in 14 type 1 DM patients showed a comparatively similar free plasma insulin profile. However insulin lispro had a faster onset of action and more rapid decline of action.

Long Acting Analogues

Traditionally available intermediate and long acting insulins like isophane, lente and ultralente do not fulfill the requirement of an ideal basal insulin i.e. providing 24 hour control with minimal variability in absorption. The development of long acting insulin analogues is based on two principles:

1. Changing the insulin pH to neutral thus allowing it to precipitate in subcutaneous tissue thus delaying absorption.
2. Binding insulin to a serum carrier with a prolonged half-life to delay its activity.

1. *Insulin Glargine*

Insulin glargine is a long acting basal analogue with no pronounced peak of activity. This is achieved by substituting an asparagine residue with glycine at position 21 of the A chain and elongating the B chain at the C terminus by adding two arginine residues. This causes the point of least solubility to shift from 5.4 to 6.7 making insulin glargine less soluble at the physiological pH of subcutaneous tissue.

As compared with NPH insulin, insulin glargine results in prolonged insulin absorption and shows little peak activity, as demonstrated by differences in disappearance curves⁷. Rates of absorption of insulin glargine at various sites do not differ. Furthermore, there is no evidence that insulin glargine accumulates after multiple injections⁸. In another pharmacodynamic study, insulin glargine was found to have no peak and to have a mean (\pm SE) duration of action of 22 ± 4 hours⁹. By way of comparison, NPH insulin reaches a peak between 4-8 hours and then falls off rapidly, with a

duration of 12 to 14 hours. Insulin glargine is administered subcutaneously at bedtime.

Trials

Numerous studies have shown the efficacy of insulin glargine in type 1 DM. In a study of 534 patients of type 1 diabetes over a period of 28 weeks treatment with insulin glargine resulted in greater reduction in FBG levels from baseline when compared to isophane insulin. Further more, fewer patients in the insulin glargine group developed symptomatic hypoglycemia or nocturnal hypoglycemia (18.2% vs 27.1%). Insulin glargine also provides effective glycemic control and is well tolerated by type 2 diabetics as evidenced by clinical trials^{10,11}.

2. Insulin Detemir

A more recent strategy in the production of insulin analogues has been to attach fatty acids capable of binding to albumin to the insulin molecule. In insulin detemir, the amino acid threonine at the B30 position on the human insulin chain is lacking and a 14 carbon fatty acid is attached to lysine at B29. Acylation of the insulin molecule with a fatty acid results in albumin binding and also increased self association of the insulin hexamers¹².

Trials

A multicenter, open, randomized trial of 59 patients with type 1 DM showed that insulin detemir was as effective as isophane insulin in glycemic control, but showed less intra-patient variability in FBG, and a more delayed onset of action. Patients treated with insulin detemir also had fewer episodes of hypoglycemia¹³.

Insulin detemir is suitable for administration in a basal bolus regimen in type 2 diabetics. The protracted pharmacological profile of insulin detemir also suggests that bedtime administration may not be mandatory. If more suitable for the patients, it can be administered earlier in the evening and still provide a sufficiently sustained insulin supply to control FBG levels without an excess risk of nocturnal hypoglycemia.

3. Premix Insulin Analogues

Two premixed insulins that contain rapidly acting analogues are available; neutral protamine lispro (insulin lispro protamine) and protamine crystalline aspart. (Basal insulin and prandial insulin are sold already mixed in a fixed ratio.) The former can be obtained in a 25 percent mixture of insulin lispro, whereas the latter is available in a 30 percent mixture of insulin aspart.

Functionally, the protamine component of these two preparations is identical to that of NPH.

Studies have shown that, as compared with a premix of 70 percent NPH and 30 percent regular insulin, the premixed analogues result in reduced postprandial hyperglycemia but no changes in glycosylated hemoglobin levels^{14,15}.

Trials

The 1-2-3 study: A 48 week, multicenter, open labelled trial in 100 patients with type 2 diabetes not achieving glycemic targets on oral anti diabetic (OAD) drugs, with or without once daily basal insulin. Patients discontinued prior basal insulin and added one injection of biphasic insulin aspart (BIAsp) 70/30 at bed time. The dose was self titrated every 3-4 days to achieve FBG of 80-110 mg/dl.

The results showed that the addition of once daily BIAsp70/30 before dinner enabled 21% of the patients to achieve AACE and IDF targets ($HbA_{1C} \leq 6.5\%$) and 41% to achieve ADA targets. With two daily injections these glycemic goals were achieved by 52 and 70% of subjects. With three daily BIAsp injections, 60% of patients achieved $HbA_{1C} \leq 6.5\%$ and 77% achieved $HbA_{1C} < 7\%$ ¹⁶.

INITIATE study: A 28 week multicenter, randomized, open labelled, treatment to target trial in 114 patients with type 2 diabetes inadequately controlled on OADs. 40% of patients taking insulin glargine once a day reached $HbA_{1C} < 7\%$. But in the group receiving BIAsp 66% reached HbA_{1C} goals of $< 7\%$ ¹⁷.

Premixed insulin analogues have a more physiologic time-action profile, can be administered closer to mealtime, and produce greater reductions in the magnitude of PPG excursions than human insulin 70/30. The development of premixed insulin analogues that are rapidly absorbed and cleared, with a more predic-table time-action profile than human insulin, has enabled insulin therapy to become more physiologic. Both basal and prandial requirements can be covered with 1 injection of the same formulation of insulin, thereby simplifying administration. Premixed insulin analogues increase flexibility and convenience of administration because they can be injected immediately before or after a meal once, twice, or 3 times daily as needed. The same form of premixed insulin can be used at different stages in the progression of type 2 diabetes. Along with these benefits, they are available in several convenient and simple insulin delivery systems. These features may improve initial patient acceptance of and later adherence to insulin therapy.

CLINICAL POSITIONING

1. Children

The use of insulin in children will continue to increase as the incidence of diabetes in this population grows¹⁸. One practical issue pertains to the use of rapidly acting analogues in school-age children, who often want snacks late in the afternoon. One option is to inject a small additional prandial dose of either insulin aspart or insulin lispro.

As compared with the findings for adults, there are far fewer data concerning the use of insulin glargine in children. No pharmacokinetic studies have been conducted in children, although there has been one report of lower nocturnal free insulin levels in children who received insulin glargine than in those who received NPH insulin¹⁹. One study of 349 children who were 5 to 16 years old showed no difference in glycosylated hemoglobin levels between children who received insulin glargine and those who received NPH insulin, although less severe hypoglycemia was observed in the group that received insulin glargine²⁰. Similar data were reported in a study involving 114 children who were given insulin glargine at bedtime and NPH insulin in the morning so that lunchtime prandial insulin would not be required²¹.

2. Pregnant Women

Data from prospective, blinded, randomized clinical trials of insulin analogues in pregnancy are lacking. However, retrospective analysis has not shown any significant difference between insulin lispro and regular insulin in regard to either fetal or maternal outcomes. Indeed, the largest amount of data regarding safety in pregnancy for any insulin analogue is for insulin lispro. One report noted that there was no transplacental passage of insulin lispro at blood levels similar to those generally evaluated with other forms of exogenous insulin therapy²².

Bhattacharyya and colleagues reported that there were no differences in gestational outcomes between a group given regular insulin (138 subjects) and a group given insulin lispro (75 subjects), although glycosylated hemoglobin levels were lower with the analogue²³. Other recent reports have reached similar conclusions^{24,25}.

The greatest concern about the administration of insulin lispro in pregnancy resulted from a 1999 report that in 3 of 10 women who received this agent during pregnancy, diabetic retinopathy developed by the third trimester²⁶. However, a more recent prospective, open-

label study involving 69 pregnant women with type 1 diabetes revealed no differences in the frequency of diabetic retinopathy between women who received insulin lispro and those who received regular insulin during pregnancy, and glycosylated hemoglobin levels were significantly lower with the analogue after the first trimester²⁷. Most experts now agree that insulin lispro can be used safely in pregnancy²⁸.

Insulin aspart in GDM

Pettitt, et al conducted a study to assess the short-term efficacy of insulin aspart in comparison with regular human insulin in women with gestational diabetes mellitus (GDM) during standardized meal tests. The study included 15 women with GDM who had inadequate diabetes control with diet alone. On 3 consecutive days, breakfast meal tests were performed—the first with no exogenous insulin and the other two after the injection of either regular insulin or insulin aspart. The results showed that the peak insulin concentration was higher and the peak glucose and C-peptide concentrations were lower with both insulin preparations than with no exogenous insulin. Glucose areas under the curve above baseline were significantly lower with insulin aspart, but not with regular insulin, than with no insulin. This study demonstrated that effective postprandial glycemic control in women with GDM who required insulin was brought about by insulin aspart through higher insulin peak and lower demand on endogenous insulin secretion²⁹.

3. Renal or Hepatic Impairment

The pharmacokinetic profile of insulin detemir has been investigated in individuals with varying degrees of renal and hepatic impairment. In renally impaired individuals, no significant differences between groups stratified by degree of impairment in any of the pharmacokinetic parameters assessed. In patients with hepatic impairment no difference to healthy individuals was found with reference to C_{max}, t_{1/2} or mean residence time.

ADVANTAGES OF ANALOGUES

1. *Reducing the threat of hypoglycemia.* Hypoglycemia is the most common side effect of insulin therapy and nocturnal hypoglycemia the most feared. The various insulin analogues are associated with decreased risk of hypoglycemia as evidence by numerous trials. This advantage parallels with their more closer physiological action profile.

2. *Weight gain:* Weight gain with insulin therapy is a common occurrence in both type 1 and type 2 diabetics and this can have deleterious consequences. A very consistent finding in all the phase iii trials comparing insulin detemir with NPH insulin is the lesser weight gain associated with insulin detemir and this is statistically significant.

The mechanism underlying this finding may relate to the greater predictability of insulin detemir in lessening the risk of nocturnal hypoglycemia and hence defensive snacking. The other mechanism postulated is that detemir has a more effective action in the CNS due to the fatty acid chain facilitating transport into the brain. Insulin then acts as a satiety signal on the hypothalamic receptors³⁰.

3. Predictability in insulin action.
4. Decreased glycemic variability across the day.
5. Consistent pharmacokinetic profile across all age ranges.
6. Superior glycemic profile.

SUMMARY

The evolution in insulins—from those produced from animal species to human-insulin preparations produced with recombinant DNA technology to the present-day insulin analogues—represents more than 80 years of collaboration among protein chemists, clinical researchers, and millions of people with diabetes. The introduction of better tools for the monitoring of glycemic control, coupled with evidence that near-normal glycosylated hemoglobin levels reduce the risk of diabetic complications, has increased the demand for insulin preparations that have greater effectiveness, safety, and versatility. Insulin analogues have met this demand, in large part, by the allowance of discrete, and therefore more accurate, replication of the basal and prandial components of insulin replacement, with an attendant decrease in the risk of hypoglycemia. The proper use of insulin analogues allows people with diabetes greater flexibility in the timing of meals, snacks, and exercise, which in turn enhances their ability to lead normal lives. Nevertheless, current insulin-replacement regimens are far from perfect; to date, it is impossible to replicate normal insulin secretion.

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