



Evolution of Modern Insulins

Siddharth N. Shah

The journey of insulin development since its discovery by the Nobel laureates Banting and Best in 1921 in itself is very interesting. Insulin therapy revolutionised the treatment of diabetes and is integral part of management of all people suffering from type 1 diabetes and many type 2. It has been a continuous endeavour for medical scientists to develop more and more new forms of insulin which can mimic the physiological insulin secretion closely and make the therapy convenient.

The importance of tight glycemic control in reducing the long term complications of diabetes was highlighted in various large clinical studies.¹ Insulin therapy can improve and maintain glycaemic control, preventing long-term complications even in type 2 diabetes.^{2,3,4}

In view of this the target goals have become more and more stringent. Today, most of the diabetes associations recommend the HbA1c levels to be as close to normal as possible. To reach these targets in all patients, insulin is the most predictable and effective option.

Over nine decades we have observed a significant change in type of insulins in the quest of simple and safer options to reach these stringent targets. With the earlier generation pancreatic insulins of animal origin we have faced various concerns due to presence of impurities, allergic reaction and non-physiological pharmacokinetics. Even with the advent of most purified human insulins produced by recombinant DNA technology fail to mimic the physiology. This problem is due to the difference in pharmacokinetics of endogenously secreted insulin and exogenously administered insulin in subcutaneous tissue.

Although human insulins have been our mainstem of diabetes management for more than last 20-30 years, we have been facing some practical problems with the human insulins. For every patient taking the regular human insulin or the human premix we need to instruct to inject insulin around 30 minutes before meals. This is so routine in clinical practice that we tend to forget the intrusion this causes in patients life. Does this story ends at this level, probably not as even putting up restrictions on patient's life, the injected insulin behaves a little too different from physiology. The absorption of insulin from the injection site is a complex process affected by many factors, such as location of the site, physical state of the patient and the nature of the insulin preparation. After subcutaneous injection of regular soluble insulin into the femoral region it takes 2-4 h for the insulin to be absorbed at maximum rate. This delay is due to the hexameric form of insulin at high concentration, which has to be enzymatically degraded to monomers in the subcutaneous tissue

before absorption. This slow rise to peak insulin concentration accounts for immediate postprandial hyperglycaemia and when the insulin concentration falls slowly after the peak, the extended period of elevated insulin concentration results in a tendency towards late (between-meal) hypoglycaemia.⁵ To bypass this slow absorption rate and avoid postprandial hyperglycaemia, regular human insulin was recommended to be injected 30-60 minutes before a meal. As a result of this there was always a risk of pre-prandial hypoglycaemia if the meal is missed or delayed making the therapy inconvenient for the patients.⁵ This usually leads to lack of compliance to timing of injection in relation to the meal and the consequent rise in postprandial blood glucose levels. All these factors make conventional soluble human insulin little far from ideal.

Intermediate-acting insulin preparations that are commonly used for basal supplementation such as NPH have a delayed onset and their action reaches a peak around 5-7 hours and lasts for about 16-20 hours. This results in a distinct peak and trough effect, causing wide variations in blood glucose levels⁶. Conventionally, we advise the basal insulin injections at night with the idea of controlling hepatic glucose output during the night time. With NPH due to the peak in its activity a few hours (5-7 hours) after subcutaneous administration, which, on evening administration, can lead to nocturnal episodes of hypoglycaemia. One other important shortcoming with NPH is the duration of action which is too short to provide full 24-h coverage with a single daily injection⁷. As with regular soluble insulins their action could vary widely not only from person to person but also within the same individual at different time points. The variability results, in part, from the fact that these formulations are all suspensions and therefore, even with vigorous mixing of the suspension prior to injection, it is difficult to maintain reproducibility of dosing⁸. In summary the main pharmacokinetic limitations of conventional long-acting insulin preparations such as NPH relate to their inability to recreate the low, peak-less, overnight plasma insulin profile of normal physiology.⁹

In general, in spite of increasing availability of human insulin preparations and their usage we still struggle to achieve the target glycemic control. The difference in pharmacokinetics of these conventional insulin preparations, their inability to closely match the physiological insulin secretion profile, variability in response & resultant questionable patient's compliance can not be denied to be partly responsible for this struggle.^{10,11,12}

The shortcomings of conventional human insulins stimulated considerable research into new methods of improving insulin therapy with more physiological and reproducible time action profiles. Until recently advances in insulin formulation were limited to improvements in insulin purity, insulin species,

Table 1 : Insulin analogues – modern insulins and their introduction

Modern Insulin	Structural modification	Introduced
Rapid – acting		
Insulin Lispro	Reversal of proline and lysine at B28 & B29	1996
Insulin Aspart	Substitution of proline at B28 with aspartic acid	1999
Insulin glulisine	Asparagine at B3 is replaced by lysine & lysine at B29 is replaced by glutamic acid	2008
Long – acting		
Insulin glargine	Asparagine at A21 is replaced by glycine; 2 arginine residues are added to the C – terminus of B chain	2001
Insulin Detemir	Threonine at B30 is removed and myristic acid (FA) is attached to lysine at B29	2004
Premix		
Biphasic insulin aspart	Contains 30% insulin aspart + 70% protaminated insulin aspart	2002
Biphasic insulin lispro	Contains 25% insulin lispro + 75% protaminated insulin lispro	2000

and adjustment of the composition of the preparation with respect to retarding agent and other excipients. Later on the efforts were focused at searching for better insulin formulations that can mimic endogenous insulin secretion more closely, so that optimal glycaemic control becomes a reality. It was the advent of biotechnology in the 1980s, the recombinant DNA technology that made it possible to 'engineer' modifications into the amino acid sequence of insulin enabling development of insulin analogues with the intention to investigate the role of the individual amino acid in the molecular assembly, biological activity and therapeutic properties.¹³ Several strategies were studied and a few of them became successful resulting in the development of modern insulins, commonly called insulin analogues.

Insulin analogues are state of the art, modern or designer insulins. More than 1000 insulin analogues have been developed, of which 20 have been tested clinically in humans¹⁴. However, only a few of them have reached the clinician. Today globally as well as in India we have all different types of modern insulins from different manufactures and among them are the rapid-acting, long-acting and the premixed formulations (Table 1).

These modern insulins are developed with an objective of overcoming the problems with conventional insulins and are not just the chance discoveries. Since their discovery and introduction in to clinical practice large number of studies are published in various journals establishing their benefits in clinical practice and supporting various claims made for the modern insulins. In general these modern insulins are considered more physiological, predictable and safe insulin preparations. In addition modern insulin like insulin detemir is also shown to have some weight neutral property. These modern insulins are now getting evaluated in special clinical situations like children, patients with renal & hepatic impairment and also in pregnancy. Some of these insulins like insulin aspart have also been approved in pregnancy based on the results of randomised clinical trials. Recently long term data studies even up to 4.5 years is published in international conference on insulin aspart evaluating its benefit in long term complications of diabetes. In addition to these various clinical trials there is large data generated on these modern insulins through global clinical experience programmes or observational studies eg. IMPROVE™, PREDICTIVE™, ATLANTUS etc.

In view of this growing body of evidence for modern insulins, it is important to look at this data critically and draw clinically meaningful conclusions. To help this objective this issue on modern insulin evaluates the clinically relevant publications

on all the currently available modern insulin preparations. This issue includes thorough discussion on rapid acting, long acting /basal and premix modern insulin preparations by various experts in the field. The issue also includes a special review on these modern insulins in pregnancy describing their current status in pregnancy and clinical efficacy profile.

This issue also focuses on one of the most controversial but most clinically relevant issue of biosimilars. This interesting article on the issue of biosimilars focuses on various aspects including inherent differences in various biosimilar preparations, possible concerns and differences in their efficacy or safety profile. It also throw's some light on the current global regulatory scenario for biosimilars.

Basal bolus regimen is the gold standard and most physiological regimen for exogenous insulin replacement. However premix insulin in India may be used when it comes to combining convenience and compliance. If used in appropriate manner with patient education it can get desired results in most of our patients. To help understand this dynamics better and to make the use of premix insulins more uniform and user-friendly a consensus document from experts across the country is the highlight of this issue. This document is focused on usage of premix insulins for better and safer glycemic control in our patients for primary care physician.

References

1. The Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–86.
2. UK Prospective Diabetes Study (UKPDS) 13: Relative efficacy of randomly allocated diet, sulfonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 1995;310:83–8.
3. UK Prospective Diabetes Study 16: Overview of 6 years' therapy of type II diabetes, a progressive disease. *Diabetes* 1995;44:1249–58.
4. Ohkubo Y, Kishikawa H, Araki E et al: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized, prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103–17.
5. Heinemann L Overcoming obstacles: new management options. *Eur J Endocrinol* 2004;151 : T23–T27
6. Oiknine R, Bernbaum M and Mooradian AD. A critical appraisal of the role of Insulin Analogues in the management of Diabetes Mellitus. *Drugs* 2005; 65:325-40)

7. Barnett AH. A review of basal insulins. *Diabet. Med.* 2003;20: 873–85
8. Roskamp RH, Park G. Long-acting insulin analogs. *Diabetes Care* 1999; 22: B109–B113.
9. Heinemann L. Variability of insulin absorption and insulin action. *Diabetes Technol Ther* 2002; 4 (5): 673–82.
10. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. *Diabetes Care* 1984; 7: 188–99.
11. Binder C (1969) Absorption of injected insulin. *Acta Pharmacol Toxicol [Suppl 2]:1–87*
12. Roy B, Chou MCY, Field JB. Time–action characteristics of regular and NPH insulin-treated diabetics. *J Clin Endocrinol Metab* 1980; 50: 475–9).
13. Brange J. The new era of biotech insulin analogues *Diabetologia* (1997) 40: S48–S53.
14. Heise T, Heinemann L, Rapid- and long-acting analogues as an approach to improve insulin therapy: an evidence-based medicine assessment. *Current Pharmaceutical Design* 2001; 7:1303–25 10