The discovery of insulin by Frederick Banting in 1921 was a landmark event of the 20th century and incredible for human life. In the next couple of years, long acting insulins like protamine zinc insulin (PZI, 1930), Neutral Protamine Hagedorn (NPH, 1946) and Lente (1952) were discovered. In 1979, the insulin was the first pharmaceutical agent to be produced by recombinant DNA technology. However, were it not the fear of hypoglycemia, diabetes would have been easy to treat!

The pharmacokinetics and pharmacodynamics of available insulins is far away from the normal physiology and are associated with severe and asymptomatic hypoglycemia and weight gain. These limitations have led to the invention of insulin analogues, which are possibly closer to the normal physiology.

**PHYSIOLOGY OF INSULIN SECRETION**

Insulin is secreted from the β cells predominantly in response to glucose in a monomeric form. The Insulin secretion from the β cells occurs in pulsatile fashion at a frequency of approximately per pulse at 20 min interval constituting basal insulin secretion and is responsible for regulating hepatic glucose output and interprandial hyperglycemia. The preprandial bursts which occur in two phases, the 1st phase occurs immediately in response to meal and lasts for 2-5 minutes, while 2nd phase lasts for 5-52 minutes and returns to basal levels within 2-4 hours after meal. Therefore in normal healthy adults 25-30 units of insulin is secreted by the β cells everyday.

**DESIGNER INSULINS**

The word designer insulin has been loosely used earlier but it has definite connotation that insulin is designed for a targeted action. For example, insulin is targeted to effect its onset of action like short acting insulin analogues like lispro or aspart that have onset of action within 5 minutes. If targeted for longer duration of action, for example long acting insulin analogues like glargine or detemir which have a duration of action of approximately 24 hours and if it is designed to target the site of action, like muscle, liver or adipocytes, (tissue specific), which may possibly be available in future.

The existing conventional insulins when injected subcutaneously have time action profile that do not match normal physiological insulin secretion. The result is rigid schedule of administration in relation to meal, frequent day time as well as nocturnal hypoglycemic episodes, interprandial snacking and weight gain. The intermediate acting insulins used as basal insulin have a definite peak which can cause hypoglycemia and their duration of action necessitates more than once daily injections. Moreover, both short acting and intermediate acting insulins are associated with marked inter- and intra-individual variations in pharmacokinetic profile therefore change in insulin administration schedule is impossible to eliminate this variability in day to day life. Because of all these limitations, there is a need for insulin analogues to mimic the normal physiology. The ideal short acting analogues should be monomeric, have onset of action within an hour and last for less than 4 hours and an ideal basal insulin should have a peakless effect, a long half life and once daily dosing.

**SHORT-ACTING INSULIN ANALOGUES**

Two rapid acting analogues lispro and aspart are available in the Indian market. The amino acid composition of lispro is identical to human insulin except
that proline at B28 and lysine at B29 are reversed. The reversal of these amino acids keeps it in monomeric form as it was deduced from structure of insulin like growth factor (IGF-1). However, in aspart, proline at B28 is substituted by aspartic acid. These have rapid onset of action within 15 minutes, peaks in 30-60 minutes and lasts for about 3-4 hours. They have proved to be safe and effective to control post-prandial hypoglycemia and closely mimics normal post prandial response. The day to day intra-individual variability is also much lower as compared to conventional regular insulins. The convenience of administration just prior to meal or sometimes even after meals provides flexibility and convenience to the patients. However, this has been refuted in a eloquent study showing that it is the ambient blood glucose levels that determine the time of administration; at higher blood glucose levels, these analogues have to be injected 30 minutes prior to meal. With these analogues, there is a definite decrease in late post-prandial hypoglycemic episodes and consequent inter-prandial snacking and weight gain. Because their action is off-set by 4 hours, there is late post-prandial hypoglycemia. The glycated hemoglobin (HbA1c) achieved with these analogues is comparable to regular insulin. Improvement in quality of life was observed in open label studies in patients with T1DM but not in double blind studies involving patients with type 1 or type 2 DM. The concerns with short-acting analogues include use in patients with advanced diabetic complications, their carcinogenic and proliferative effects and their use in pregnant women with diabetes. So to summarize, minor benefits of short-acting analogues, in majority of diabetic patients, are achieved at much higher cost of therapy. Despite these limitations, they are useful in patients with gastroparesis, where it can be injected even after meals, persons with erratic food habits particularly children and elderly individuals. There is no point of using these short-acting analogues as infusion in patients with diabetic ketoacidosis (DKA), as their onset of action is only modulated when given subcutaneously.

LONG-ACTING INSULIN ANALOGUES

The long-acting analogues glargine and detemir are available in our country and are in use for sometime. Insulin glargine differs from human insulin in that the amino acid asparagine at position 421 is replaced by glycine and two arginines are added to c-terminus of the B-chain. It is a clear solution at pH of 4.0. Following subcutaneous injection, the acidic glargine solution forms microprecipitates in alkaline pH of the subcutaneous tissue, and from these microprecipitates it slowly dissociates to monomers and being absorbed across the capillaries. The onset of action is within 2 hours with peakless duration of action lasting upto 24 hours. Glargine should not be diluted or mixed with any other type of insulin. When compared with bedtime NPH insulin, glargine was associated with less nocturnal hypoglycemia (12.6% insulin glargine vs 28.8 NPH p = 0.011). However, in practice when nocturnal hypoglycemia occurs with bed time glargine, the timing of insulin glargine should be changed to morning injection. However, there is no difference in target HbA1c achieved and weight gained during treatment between insulin glargine and NPH. The low risk of nocturnal hypoglycemia with insulin glargine is achieved at a cost of Rs. 2.5/- approximately per unit of glargine in comparison to Rs. 0.35 per unit of NPH. Though nocturnal hypoglycemia is a major constraint to achieve HbA1c < 7%, therefore, insulin glargine is quite useful to accomplish these targets. The various unresolved issues with insulin glargine include frequency of administration, safety in children and pregnant women, safety and doses modifications in patients with renal failure. Insulin detemir is also another basal insulin but differs with insulin glargine in pH as being neutral, and can be mixed with other insulins. The amino acid threonine at B30 is replaced by myristic acid, a C14 fatty acid in detemir. After absorption it binds to albumin in the plasma via fatty acid chain. Detemir has approximately 20 hours of duration of action and so needs to be given twice daily. However, in long term use, its duration of action exceeds more than 20 hours therefore, a single daily injection is usually sufficed. As with glargine, the risk of hypoglycemia is significantly reduced with detemir in comparison to NPH. Preliminary evidence suggest that there is no weight gain or rather weight may decrease with detemir, and whether this is a result of decreased risk of hypoglycemia or selectively modulating the appetite center is not clear.

NON-INVASIVE INSULINS

Despite the well established benefits of tight glycemic control, not only on the part of patients but as well as on physicians there is reluctance to inject insulin. Therefore, researchers have always been on developing newer non-invasive insulins. Inhaled insulins are now available for clinical use and shows promising results. Pulmonary insulins has an anatomic advantage of vast surface area and well perfused absorptive surface. Also alveolar tissues lacks peptides thus eliminating the concern of first past
metabolism. After inhalation of insulin, peak concentration reaches within 15-40 min mimicking short acting analogues thereby making it a pre-meal insulin. However, bio availability was low varying between 20-25% as compared to subcutaneous insulin. A meta-analysis involving randomized controlled trials, 3 with patients of T1DM and 3 with patients of T2DM, showed that inhaled insulin along with basal insulin was associated with comparable levels of HbA1c, hypoglycemic episodes and better compliance and quality of life. However, exorbitant cost, lower bio availability and atleast one prick of basal insulin is must for regulating nocturnal hepatic glucose-output are important issues.

Another non-invasive mode of delivery of insulin is oral route. However, major limitations in formulating oral insulin is gastro-intestinal degradation of insulin by peptidases, lack of selective channels for absorption of insulin thereby requiring high doses to achieve measurable insulin levels. The most promising oral insulin to date is hexyl-insulin-monoconjugate-2 (HIM-2), a native recombinant insulin with a small polyethylene glycol 7-hexyl group attached to position B29 amino acid lysine. HIM-2 has a bio availability of 25% with acceptable glucose lowering effect has been shown in phase I and II clinical trials. Another oral insulin include oral buccal delivery system delivering a liquid aerosol formulation of insulin (oralin). To date, no long term safety data are available and efficacy studies are limited.

In conclusion, newer insulin analogues are useful in defined subsets of patients. Short acting insulin analogues are useful particularly in patients with gastroparesis, patients with erratic food habits and patients in intensive care unit setting. Long acting insulin analogues are useful in those with marked glycemic excursions, patients with risk of hypoglycemia particularly elderly individuals or with long standing diabetes and where there is a vigorous need to achieve HbA1c <7%. However, the ideal basal-bolus insulin combination, which exactly mimics normal 24-hour physiological insulin secretory pattern, is yet to be developed.

REFERENCES


