REVIEW ARTICLE

What is new in insulin-really new?

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The UKPDS (United Kingdom Prospective Diabetes Study) and DCCT (Diabetes Control and Complications Trial) have firmly established the role of blood glucose control in preventing and slowing the progression of microangiopathic complications in type 2 and type 1 diabetes respectively. Among the armamentanium of drugs available to control glycemia, insulin is the most efficacious. However, currently available human insulin cannot mimic the normal physiological insulin secretion. Hypoglycemia and weight gain are the major constraints with intensive glycemic control to achieve the target HbA_{1c} level. These limitations have led to the inventions of insulin analogues or 'designer' insulin with profile that more closely mimic normal insulin secretary pattern. Long term analogues being peakless has the advantage of having minimum nocturnal hypoglycemia episodes and are helpful in achieving the target HbA_{1c} level of <7%. Short acting analogues have advantage over existing regular insulin by having smooth control of postprandial hyperglycemia. However, the cost of these newer insulin analogues is prohibitive, furthermore long term safety data of their potential carcinogenic and proliferative effects on microvasculature are not available and limited data is available regarding their use in pregnant women with diabetes. Because of search for alternative non-invasive delivery methods, oral, pulmonary (inhaled), buccal or even transdermal insulin delivery systems are on the horizon.

KEY WORDS: Alternate insulin, designer insulin, hypoglycemia.

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Introduction

The discovery of insulin in 1922 by Frederick Banting and his colleagues at the university of Toronto was one of the greatest medical breakthrough of the 20th century. In fact, a headline appeared in a newspaper called Banting "the conqueror of diabetes."[1] In the next few years long acting insulins like protamine zinc insulin (1930), Neutral Protamin Hagedorn i.e., NPH (1946) and insulin zinc i.e., Lente (1952) were discovered. In the year 1975 the first premixed insulin was launched. Advances in chromatography in 1960 and 1970 led to the production of more highly purified insulins. In 1979, human insulin became the first pharmaceutical agent to be produced by the recombinant DNA technology.[1] However, were it not the fear of hypoglycemia, diabetes would have been easy to treat. The pharmacokinetic of dynamic profile of these insulins were far away from the normal physiology. These limitations has led to the inventions of insulin analogues or designer insulin (1987) with profile that more closely mimic normal insulin secretory pattern.[2] However, all these insulin preparations needs to be give by SC or I.V. injection, thus limiting the patient's acceptability. Because of the search for alternative delivery methods, oral, pulmonary (inhaled), buccal or even transdermal insulin delivery systems are on the horizon.[3]

Designer insulin

Designer insulin means insulin deigned for a targeted action, which include modifying the duration of action i.e., short acting and long acting insulin analogues, insulin designed to target the site of action (tissue specific) i.e., muscle, liver, adipose tissue. Short acting insulin analogues include lispro, aspart and glulisine, while long acting insulin analogue include glargine and detemir.[4]

Natural β-cell only produces monomeric insulin at a

varying rate of about 0.5 to 1 U/hr in adults without diabetes. This secretion maintains serum concentration at 5 to 15 microunits / ml. Secretion occurs continuously throughout the day to suppress hepatic glucose output with distinct peak after the meal to maintain the blood glucose constantly within normal physiological range. This preparandial insulin rise occurs immediately with meal i.e., 1st phase which lasts for 2-5 minutes and as 2nd phase which last for 5-52 minutes and results in insulin concentration of 60 to 80 microunits / ml. Insulin concentration however returns to basal levels within 2-4 hours after the meal.[5]

The goal of exogenous insulin regimen in patients with diabetes is to provide physiologically mimicking correct insulin profiles. However, the existing conventional insulins when injected subcutaneously have time-action profile that do no 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, and weight gain. The intermediate acting human insulins used as basal insulin have a definite peak which can cause hypoglycemia and their duration of action necessitates more than once daily injection.[6] Because of all these limitations, insulin analogues have been the need of time. The ideal short acting analogue should have a time action profile with onset of action in less than an hour, duration of action less than 4 hour, and ideal basal insulin would have a peakless effect, a long half life and once daily dosing.

Two rapid-acting analogues lispro and aspart are available in Indian market and the third one glulisine will be available in the near future. The amino acid composition of lispro is identical to that of human insulin except that the position of amino acid proline at B28 and lysine at B29 are reversed.[7] In aspart, proline at B28 is substituted by aspartic acid and in glulisine aspargine at B3 and lysine at B29 is replaced with lysine and glutamine respectively.[8] All three have rapid onset of action (15 minutes), which peaks in 30 to 60 minutes and lasts for about 3-4 hours. They have proved to be an effective and safe postprandial insulin analogues with a time action profile that closely mimics normal post-prandial insulin response. Furthermore the intra-individual variability in time to maximum serum insulin concentration is significantly less in comparison to conventional rapid acting insulin preparations. The recent head to head trials have shown that pharmacokinetic and pharmacodynamic profile of insulin aspart and lispro were identical in adult patients with type 1 diabetes, however other studies have found minor differences.[9,10] Insulin aspart was shown to be as effective when administered preprandially and postprandially in a study in patients with type 1 diabetes.[11] This could prove valuable especially in diabetic patients with gastroparesis where insulin is often administered after meals as these patients often vomit the recently ingested food. Insulin glulisine has a unique property of activating the IRS-2 signalling pathway. IRS-2 pathway play a crucial role in pancreatic β-cell growth and survival.[12] Further studies are needed to characterize the true advantage of insulin glulisine over insulin lispro or aspart. Although the overall glycemic control as assessed by HbA_{1C} may or may not differ with the use of rapid acting insulin analogues compared with regular insulin, but their convenient administration allows more flexibility to those who eat unplanned meals or snacks especially among children and busy professional adults. Because of short duration of action the interprandial hypoglycemia is less, thus decreasing the interprandial snacking and weight gain as compared to regular insulin.[13,14] A recent metanalysis of short acting analogues versus regular insulin in forty two randomized controlled trials in 7933 patients with type 1 diabetes mellitus, type 2 diabetes and gestational diabetes mellitus showed only a minor benefit to hemoglobin A_{1C} values in adult patients with type 1 diabetes mellitus but no benefit in the remaining population with type 2 or gestational diabetes from short acting analogue treatment. The weighted mean difference between hemoglobin A_{1c} values between the two was 0.12% (95% confidence interval, -0.17 to -0.07%) for adult patients with type 1 diabetes mellitus and -0.02% (95% confidence interval, 0.10 to 0.07%) for patients with type 2 diabetes mellitus. The standardized mean difference for overall hypoglycemia (episodes per patient per month) was -0.05 (95% confidence interval, -0.22 to 0.11%) and -0.04 (95% confidence interval, -0.12 to 0.04) comparing short acting insulin analogues with regular insulin in adult patients with type 1 and type 2 diabetes mellitus, respectively. No difference between treatment were observed in children with type 1 diabetes, pregnant women with type 1 diabetes mellitus and women with gestational diabetes. Improvement in quality of life was observed only in open label studies in patients with type 1 diabetes mellitus but not in double blind studies involving patients with type 1 or type 2 diabetes mellitus. The short acting analogues are however with many concerns. There is no trial of their use in patients with advanced diabetic complications. Long term safety data of their potential carcinogenic and proliferative effects are not available and limited data is available regarding

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.

Rapid acting analogues are also available in pre mixed preparation with rapid and intermediate insulin activity. Two premixed analogues of lispro and aspart i.e. Humalog mix 75/25 and Novolog mix (70/30) are available in the Indian market. Humalog mix improved postprandial glycemic control after morning and evening meals but did not improve the overall HbA_{1C} value. This suggest that premixed insulin can be used for convenience in patients with already stable glycemic control and that rapid acting analogues improves postprandial hyperglycemia. However, no study looked at issue that for individuals eating large lunches (e.g. >40% of their total daily calories), a 70% NPH/30% regular insulin would be a better alternative. The only problem is that lunch time meal needs to be consumed at about same time each day to avoid hypoglycemia. A recent study in subjects with poorly controlled type 2 diabetes on oral hypoglycemic agents showed that initiating insulin therapy with twice daily biphasic aspart (Novolog mix 70/30) was more effective in achieving HbA_{1c} targets than once daily glargine, especially in subject with HbA_{1c} >8.5%.[17] This is consistent with the fact that as β-cell function declines, HbA_{1c} rises, and basal insulin replacement alone is insufficient to control postprandial hyperglycemia.

The conventional long-acting and intermediate acting insulins that have been used for basal control have pharmacokinetic profiles that make them difficult to use. Insulin glargine and insulin determir (soon to be available) are long acting analogues. Insulin glargine differs from human insulin in that the amino acid aspargine at position A21 is replaced by glycine and two arginines are added to C-terminus of the B-chain. It is a clear completely soluble solution at pH of 4.0. Following subcutaneous injection, the acidic glargine solution is neutralized (alkaline pH of subcutaneous tissue) and forms microprecipitates from where it is slowly dissociated to monomers capable of being absorbed across the capillaries. The onset of action is approximately within 2 hours with flat or peakless duration of action lasting upto 24 hours. Glargine should not be diluted and mixed with any other type of insulin.[18] When compared with bedtime NPH insulin, glargine was associated with less nocturnal hypoglycemia (12.6% insulin glargine versus 28.8% NPH, P=0.011).[19] However, in practice nocturnal hypoglycemia can occur with bedtime insulin glargine and when hypoglycemia occurs the timing of insulin glargine has to be changed to morning injection. This is consistent with the findings of recent study that insulin glargine can be given at any time of the day as long as it is administered at same time every day and nocturnal hypoglycemia occurred in significantly fewer patients in breakfast group.[20] Another study published recently had suggested that rapid acting insulin analogues along with glargine result in glycemic control comparable with that achieved with continuous subcutaneous insulin infusion (CSII). However, in the CSII group there was significantly greater reduction in mean amplitude of glycemic excursions and insulin requirement than in the insulin glargine group.[21] Although duration of action of glargine was 24 hr, waxing effect can be seen as early as 15 hours and some patients need two doses of insulin glargine in a 24 hour period. However, there is no evidence that this twice daily glargine has any advantage over conventional twice daily NPH insulin. The low risk of hypoglycemia and weight gain associated with glargine in comparison to NPH is achieved at a significant cost of Rs. 2.5/- approx per unit of glargine in comparison to Rs. 0.35/- approx. per unit of NPH. The various unresolved issues with glargine include ideal frequency of administration, safety in children and pregnant women, long term safety and any dosage modification in patients with renal failure.[22] Insulin determir is another basal insulin analogue soon going to be available in India. It has a neutral pH 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.[23] In comparison to NPH insulin in type 1 diabetic patient on basal bolus regimen using pre-meal rapid acting insulin apart, insulin detemir was associated with significantly reduced risk of hypoglycemia.[24] Also preliminary evidences suggest that weight gain associated with insulin therapy may be avoided when detemir is used, however whether this is a result of decreased risk of hypoglycemia or is secondary to a selective appetite-modulating effect of it is not clear at present.[25]

Non-invasive insulins

Over the years need for non-invasive insulin were strongly felt because of reluctance both on part of physicians and patients to initiate insulin therapy despite the well established benefits of tight glycemic control. Pulmonary delivery of insulin appears to be the first reported alternative to injections.[26] Pulmonary route

of administration has an anatomic advantage of vast surface area (50-140 m^2, 500 million alveoli) and well perfused absorptive surface. Also lung lacks certain peptidases that are present in gastrointestinal tract, thus eliminating the concern of first pass metabolism. Because of presence of very thin alveolar-capillary barrier, absorption is rapid and onset of action is quick after inhalation with a peak plasma concentration being reached 15-40 minutes after absorption, mimicking like insulin aspart, thereby making it an ideal pre-meal insulin. However, bioavailability was low, between 20-25% of that associated with subcutaneous insulin. The various pulmonary delivery insulin currently under development include exubera, a fine dry powder formulation (< 5 µm in diameter) of regular short-acting human insulin. The insulin dry powder is packaged into a single dose blister containing 1 or 3 mg with 1 mg blister corresponding to approximately 3 units of insulin. The early studies demonstrated reproducible pharamcokinetics and postprandial control with this device comparable to subcutaneous regular insulin. A 24 week phase III study involving 298 patients with type 2 diabetes showed comparable HbA_{1c} with subcutaneous insulin regimen.[27] A meta-analysis involving 6 randomised control led trials, 3 with patients of T1DM and 3 with T2DM showed that inhaled insulin along with basal insulin was associated with better compliance, patient satisfaction, quality of life and comparable levels of HbA_{1c} and hypoglycemic episodes when compared with basal bolus insulin regimen.[28] Various other pulmonary delivery devices include AERx developed by Aradigm and now in collaboration with Novo-Nordisk. At present, however, no data on pulmonary safety is available and high cost, lower bioavailability are other important issues.

Another non-invasive mode of delivery for insulin is oral route.[29] However, major limitation in formulating oral insulin is gastric enzyme degradation resulting in poor gastrointestinal absorption of insulin molecule. Another barrier is that no selective transport mechanism exists for insulin in gastrointestinal tract, so extremely high doses are needed to achieve some measurable insulin absorption. Other barrier include unpredictable transit time and delayed absorption of encapsulated insulin. All these factors may explain the low bioavailability (0.5%) of oral insulin. The most promising oral insulin to date is hexyl-insulin-monoconjugate -2 (HIM2), a native recombinant insulin with a small polyethylene glycol 7-hexyl group attached to position B29 amino acid lysine. Ongoing phase I and II clinical trials suggest that oral HIM2 has a bioavailability of 25% and result in an acceptable glucose-lowering effect. Another oral insulin include oral buccal delivery system delivering a liquid aerosol formulation of insulin or a metered dose inhaler (Oralin). It is a recombinant human insulin with added enhancers, stabilizers and a non-chloroflurocarbon propellant. To date, no long term safety data are available, efficacy studies have only been presented as abstracts, and all these abstracts did not assess the side effects.[30]

Conclusions

Newer insulin analogues are more expensive, long term safety is not known and their use in children and pregnant women are not well established. Short acting insulin analogues provide flexibility and prevent postprandial glycemic excursions. Long acting analogues are useful in achieving target HbA_{1c} (<7%) at lesser hypoglycemic events with improved quality of life. Novel insulin analogues are promising 'designer drugs' still far away from mimicking the normal physiology. The ideal basal bolus insulin combination, which exactly mimics normal 24-hour physiological insulin secretary pattern, is yet to be developed.

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