Newer Insulin Analogues: Are They Different?

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INTRODUCTION

The advent of Insulin almost 80 years ago revolutionized treatment of diabetes and must be one of the most outstanding achievements of the twentieth century medicine. Since then there has been an ever-increasing awareness and acceptance of the need to achieve and sustain near-normoglycemia to delay onset and retard the progression of diabetic angiopathy. Physiological insulin replacement is therefore central to management of patients with diabetes. Insulin formulations, treatment strategies and method and routes of delivery have changed a lot. Both type 1 and type 2 diabetics are treated with more aggressive insulin therapy than previously. Parallel development in glucose sensing technologies has clearly shown the current short-comings of implementation of insulin therapies. The therapeutic concept of "Intensified Insulin Therapy" aims at mimicking the complex pattern of endogenous insulin secretion in patients with diabetes using subcutaneous injections of short-acting insulin before meals (to mirror prandial insulin secretion) and of retard insulin preparations once or twice daily (to mimic basal insulin secretion). Unfortunately, the time action profiles of currently available insulin preparations are far from being optimal. Consequently, both clinical diabetologist and patients called for the development of insulin preparations with more adequate time-action profiles. The pharmaceutical industry has tried to fulfill this demand by the development of insulin analogues. The use of insulin analogues is rapidly expanding, at present in our country there are two short-acting analogues available for practical use, insulin aspart and insulin lispro and one long-acting analogue, insulin glargine. Another long-acting analogue, insulin detemir is yet to come to the market. This review is aimed at comparing these newer pharmacological agents in practice and ascertain the validity of claims made by the industry.

WHAT IS THE NEED FOR COMPARISON?

The response from the clinical diabetologist is highly variable with the use of analogues, although both short-acting and long-acting analogues promise to fulfill all the shortcomings of the previous insulins, surprisingly the new fast-acting analogues have not achieved the expected commercial success[1] which emphasizes the need for new strategies for basal insulin supplementation, exercise, diet and blood glucose monitoring. There are three basic issues for which analogues are considered: 1) Post-prandial hyperglycemia, 2) Nocturnal hypoglycemia, 3) Fasting hyperglycemia. Other issues of less importance are 4) Soluble insulin to be given 30 mins. before meals, too inconvenient or difficult. 5. The meal size is large or has more calories. 6. Meal timings are variable. 7. Evidence of significant HbA_1C improvement is lacking. In addition to these issues, safety concerns also needs to be addressed. The safety issue was raised for the first time[2] when one of the first rapid acting analogues developed for clinical use Insulin B 10Asp, caused cancer in animal studies. This is of special concern, as B10Asp, like lispro and glargine showed increased binding to the insulin-like growth factor (IGF)-1 receptor in osteosarcoma cells.[3] However it has since been elucidated that the carcinogenicity of B10Asp was not mediated by the increased binding to the IGF-1 receptor but rather to a slower dissociation from the insulin receptor. In addition, a concentration more than 1000-fold above the physiological concentration would be necessary to reach a 50% receptor binding of the analogues at the IGF-1 receptor.[4] Indeed, the mitogen-metabolic potency ratios of insulin analogues were found to be inversely and exponentially correlated with the insulin receptor dissociation rate constant (kd)(r=0.99). Insulin analogues with kd values of < 40% showed a disproportionately greater increase in mitogen rather than in metabolic potential.[5]

EVIDENCE-BASED MEDICINE

Using the criteria of evidence based medicine there is good evidence (evidence level I or II) for improvement if HbA_1C and hypoglycemia with insulin lispro and insulin aspart. Although both analogues have been repeatedly shown to act more "physiologically"(i.e. with a more rapid onset and shorter duration of action) than human regular insulin, the benefits demonstrated so far concerning HbA_1C and hypoglycemia are only modest and smaller than might have been expected based on theoretical considerations and phase1 clinical trials. The hope is both these analogues will prove superior to the previous insulins in improving patient oriented outcome parameters and it will largely depend on the judgment of a clinical diabetologist, when and how to use them. However the small and consistent improvements with insulin analogues demonstrated so far appear to justify the use as treatment options in patients with diabetes, especially in view of their apparent clean safety profile.

It seems conceivable that in individual patients the benefit of insulin analogues is higher than is reflected in changes observed in large trials.[6] We need to design appropriate trials in Indian subjects to test whether or not special patient sub-groups benefit particularly from the more physiological time-action profile of insulin analogues. This is particularly so because of differences in the dietary practices in Indian subjects and carbohydrate loads which vary in lunch and dinner. Recent investigation of post-prandial injections of fast-acting analogues[7] in type 1 diabetic patients with renal impairment has shown promising results. Randomized trials have not answered the question of which individuals actually benefit from medical interventions. This, surely, is the key issue in clinical research for these analogues.

RAPID-ACTING INSULIN ANALOGUES

One way to achieve a faster absorption of s.c. insulin for better prandial insulin replacement, is to decrease the degree of self-association of insulin molecules. This can be achieved by specific modification of the primary structure in certain areas of the insulin molecule. By means of recombinant DNA technology, the insulin molecule can be modified at almost any position, its amino-acid sequence leading to insulin analogues with different properties. By reversal or removal of certain amino-acids in these areas, the self-association of the insulin molecules can be reduced or prevented for instance, at a neutral pH uncharged amino-acids are substituted with amino-acids with a negative electric charge, this impairs self-association. On the other hand it is also possible to generate insulin analogues in which the cohesive forces to form hexamer are increased, thereby making it difficult to dissociate the substitution of one amino-acid in certain areas of the insulin molecule, this impacts not only the absorption rate, but also other biological properties of insulin which may even be undesirable or even dangerous.

Among the large number of theoretically conceivable insulin analogues, more than 1000 have been developed, viz. but only 20 have been tested for clinical efficacy in humans so far. In recent years five rapid-acting analogues have been developed, viz. B28LysB29Pro – Insulin lispro, B9AspB27Glu, B10Asp, B28Asp viz. – Insulin aspart, B3LysB29Glu – HOE 1964.

Out of these, insulin lispro and insulin aspart are available in the Indian market. Both lispro and insulin aspart can be mixed with long-acting human insulin preparations like NPH immediately before injection. Over a longer period of time however, an exchange between the protamine-retarded human insulin (NPH) and the analogue would occur (resulting in a mixture of free analogue, free regular insulin, retarded insulin and retarded regular insulin). To overcome these problems, specific protamine-related preparations of lispro and aspart insulins have been developed. This allows the formulation of fixed mixtures of fast-acting insulin analogues and retarded insulin for the use in type 2 diabetic patients.[8,9]

LONG-ACTING INSULIN ANALOGUES

Various approaches are used to retard the absorption and thus the metabolic action of insulin. This includes shift of the isoelectric point of insulin (i.e. the pH at which insulin is least hydrosoluble) by substitutions of amino acids at the C-terminal portion of the B-chain from 5.4 to a neutral pH of 7.4. After injection of acid preparations of these insulins, in which the insulin is available in solution (and not a suspension like NPH insulin)[10-12] there will be a precipitation of relatively small crystals having a similar size at a physiological pH in the subcutaneous depot.

In insulin glargine, two arginines are affixed to the C-terminal portion of the B-chain and aspargine is substituted with glycine at position A21 (end of the A-chain) i.e. Gly(A21)-Arg_2 (B31-B32) of human insulin to improve the stability. Another retarding mechanism employed within this analogue (apart from shifting the isoelectric point is an enhancement of the cohesive forces between the six insulin molecules of a hexamer ("crystal contact engineering"). The intermolecular distances between the monomers in insulin glargine are shorter than in human insulin. It is necessary to add a greater amount of zinc (0.5 -2μg/IU) to obtain a stable preparation, because of its acidic pH of 4.0 and its excess of zinc, insulin glargine cannot be mixed with neutral regular insulin, as this would result in an immediate change of pH and of the binding of zinc with the subsequent alterations of the time-action profile of both insulin glargine and regular insulin.[13]

Comparison of time-action profiles of lispro and aspart insulins

Most studies with comparable experimental design (employing the glucose-clamp technique) and subject selection, a more rapid onset of action, a shorter time to peak activity and a shorter duration of action was shown for both analogues compared to regular insulin.[14] However there are not many studies to compare lispro with aspart as of today.

A multi-centric study of 90 male subjects with type 1 DM which was a randomized double-blind crossover study under chief investigator Philip Home as UK aspart study group [15] has compared insulin aspart with human insulin and has concluded-''In comparison with human insulin, insulin aspart can improve post-prandial control as assessed by a reduction in hyper and hypoglycemic excursions in people with type 1 diabetes. For its full potential to be realized, it will need to provide better control of night time hyperglycemia". This means only control of post-prandial glucose is not adequate and therefore benefits of short-acting analogues can be derived only if you can also use long-acting insulin at bedtime effectively.

Comparison of time-action profiles and clinical benefits of long-acting insulins

After reviewing many studies selected from MEDLINE search carried out using the keywords "insulin detemir", "insulin glargine", "NPH insulin", "lente" or "ultralente', the search was limited to years 1987-2002 and to randomized controlled trials in humans, English language only. This search yielded 137 papers, from these clinical trials comparing two or more basal insulin were selected, NPH was the comparator, this yielded 12 published studies. An additional search of abstracts from recent ADA and EASD congresses (2001-2003) was carried out for insulin detemir. All these studies are summarized in a review article of Anthony H. Barnett.[16] Most studies compared the changes at end-point vs baseline in following parameters HbA_1C, FPG and FBG, incidence of hypoglycemia (symptomatic and nocturnal). The clinical experience in type 1 diabetes shows that glargine offers equivalent improvements in HbA_1C but

significantly lower FBG and FPG as compared to NPH. The nocturnal symptomatic hypoglycemia was less pronounced when insulin glargine was compared with twice daily NPH insulin.[17] Overall incidence of nocturnal hypoglycemia is much lower in patients treated with glargine. Most of the papers have clearly demonstrated a lesser glycemic control which could be due to the fact that the dosage was adjusted and titrated for reduction of incidence of hypoglycemia rather than only to reduce HbA_1C, FBG and FPG. More studies are required to ascertain the full potential of glargine towards HbA_1C reduction (as per ADA directions), the reports on insulin detemir are promising. Some disadvantages associated with insulin glargine therapy include increased cost, increased pain at injection site and inability to mix with other insulin products. Optimal therapy with insulin glargine may require increasing the total daily dose of rapid-acting bolus insulin analogues to achieve glycemic control. The use of glargine should be reserved for those who continue to have elevated morning blood glucose levels and episodes of nocturnal hypoglycemia while taking a combination of oral agents or a combination of bedtime NPH insulin with oral agents.[18]

Insulin Detemir

Covalent acylation of the amino group of LysB29 promotes reversible binding of insulin to albumin thereby delaying its reabsorption from subcutaneous tissue and also, possibly because of the size reducing the rate of transendothelial transport. Deletion of the adjacent ThrB30 amino-acid residue further increases albumin binding. Detemir like glargine is a clear solution.

Premixed Preparations

It is possible to mix rapid acting analogues with NPH insulins and there are many premixed formulations of insulin lispro and neutral protamine lispro (NPL) i.e. (75/25, 50/50, 25/75). Premixed insulin aspart 30% and its protamine suspension (biphasic insulin aspart 30). The efficiency and safety of these formulations is yet to be compared in Indian subjects.

CONCLUSION

These new therapeutic agents are promising a better quality of life to our diabetics, but at a very high cost and the difference in the HbA_1C and fasting and post-prandial blood glucose control is also marginal. Although the long-acting analogues have an edge over NPH in reducing symptomatic and nocturnal hypoglycemia. These newer insulins must be used judiciously while emphasizing the need for a disciplined life and merits of correct diet and regular exercise. Long term clinical trials are required to be conducted before we recommend them for use in a special group of patients. Just merely they are available is not a justification to change from human insulin. If glycemic control is poor, more efforts need to be made towards optimizing diet and increase exercise level rather than blaming previous insulin and oral agents.

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