Newer Insulins: Making Early Insulin Initiation Safer and Simpler

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Introduction
In recent times, there have been two striking developments in the area of insulin therapy. On the therapy front, insulin therapy especially in type 2 diabetes has become a topic frequently reviewed in literature (Marre, 2000; Korytkowski, 2000). These reviews discuss the role of early insulin initiation in the light of the growing burden of type 2 diabetes coupled with the need for tighter control to prevent long-term complications. According to these reviews and also published data from Indian studies, barriers to early initiation include the fear of hypoglycemia, compliance issues related to meal-time injections and fear of injection itself. Interestingly, the other striking development on the insulin formulation front designer, newer insulin analogues, inhaled insulin, oral insulin appears to be addressing these very issues which are preventing the usage of insulin even when indicated as in the case of insulin-requiring type 2 diabetes patients. The role of insulin in Type 1, Gestational Diabetes, Secondary diabetes is unequivocal.

Each of the barriers to insulin therapy outlined above can be traced to the shortcomings of available insulins viz., the delayed onset and the longer duration of action which is why designer insulins have been inserted. Several newer insulin analogues available only now in India viz., insulin aspart, insulin lyspro and premix analogue/biphasic insulin aspart, insulin glargine etc which have been designed to overcome both these barriers. Even newly purified bovine & porcine insulin as strictly speaking insulin analogues (Table 1).

For 60 years the animal pancreas was the only source from which insulin could be produced in sufficient quantities to cover therapeutic needs. Now even high yield beef and porcine pancreas with newer purification technology has made cost per kilogram of this insulin cheaper. During the late 1970s advances in recombinant DNA technology made it possible to produce human insulin biosynthetically (Goeddel et al, 1979). In 1980 the first humans received injections of human insulin combined from A- and B-chains expressed separately in E. coli with chemically prepared genes (Keen et al, 1980), and in 1982 biosynthetic human insulin became the first marketed human health-care product derived from recombinant DNA (rDNA) technology. rDNA technology insulin comes from two essential sources namely E.coli models and yeast based models. Currently, Eli Lilly markets E.coli based, while Novo Nordisk, Aventis and Wockhardt makes yeast based insulin. There is no difference on the clinical
efficacy and safety of E.coli or yeast based insulin, though yeast based insulin is cheaper to make and has a better 3-D structure than the classical E.coli model. The analogues are made also by only 3 companies from either E.coli or yeast based source. This novel technology opened new ways for the development of insulin analogs or ‘designer insulins’ with changed amino acid sequences, and hence new structural, physicochemical and biological properties. Currently we are looking at inhaled or oral insulin.

**Rationales and Strategies for Designing Insulin Analogues**

**Design Strategies**

These have entailed strategies to reduce self-association for the rapid-acting analogues and strategies to retard action for the longer-acting analogues. The former include the techniques of charge repulsion (examples: B9Asp, B12 Glu, B28Asp/insulin aspart), steric hindrance (deletion or reversal) (example: insulin lyspro), removal of metal-binding sites (examples: B10Asp, B10Thr) and hydrophilicity into hydrophobic interfaces (example: B16Glu, B26Glu). The latter include increasing isoelectric point (towards neutral) (example: Insulin Glargine) and binding to albumin of insulins acylated by fatty acids (example: Insulin Detemir).

**Animal Analogue Insulin (Highly Purified Variant)**

Human insulin was introduced without sufficient evidence and all short coming of old animal Insulin are now overcome by newer purification methodologies. Currently available Bovine and Porcine Insulin are true physiological evidence based insulins. They are cost effective but are rapidly withdrawn globally. However, patient support groups like IDDT-Insulin Dependent Diabetes Trust in UK have kept them alive. In all the developing countries they are still available, efficacious and safe as both human and analogues and are possibly safer in pregnancy than human or analogues. The cost and economics dictates insulin use in resource limited countries like India, though physician practice is to prescribe human or analogue insulin, which not necessary evidence based (Lyspro, Aspart, Glargine).

**Rapid-Acting Analogues (Lyspro, Aspart, Glucine)**

Many of the inherent properties of native insulin appear to have evolved in response to the requirements of biosynthesis and storage in the pancreas. Thus, insulin molecules in neutral solution at high concentration tend to form dimers and hexamers, which ensure stability during storage within the β-cell granule. However, because insulin binds to its receptor as a monomer, this property is not necessary for the biological activity of the hormone. The fact that insulin in concentrated, neutral solution associates into dimers and hexamers (Fig. 1a & Fig. 1b) (Brange et al, 1988), leading to a delay in the absorption of subcutaneously injected regular human insulin, led to the idea that an insulin preparation with reduced propensity to self-association might be more rapidly absorbed and

<table>
<thead>
<tr>
<th>Source</th>
<th>Rapid/Short Acting with Cost</th>
<th>Intermediate/Long Acting with Cost</th>
<th>Availability in India U-40/U-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Analogues Bovine/ Porcine</td>
<td>Regular B (Rs.70/- U-40)</td>
<td>NPH, Lente B (Rs.70/- U-40)</td>
<td>U – 40</td>
</tr>
<tr>
<td></td>
<td>Plain P(Rs100-120/- U-40 )</td>
<td>NPH, Lente P (Rs.110/- U-40)</td>
<td>U – 40 or U – 100</td>
</tr>
<tr>
<td>Human rDNA</td>
<td>Regular (Rs.140/- U-40)</td>
<td>NPH, Lente B (Rs.70/- U-40)</td>
<td>U – 40</td>
</tr>
<tr>
<td></td>
<td>Plain (Rs.140/- U-40)</td>
<td>NPH, Lente P (Rs.110/- U-40)</td>
<td>U – 40 or U – 100</td>
</tr>
<tr>
<td>Designer Analogues</td>
<td>Lyspro (Rs.350/- U-40)</td>
<td>Glargine(Rs.2500/- 1000 IU)</td>
<td>U - 100</td>
</tr>
<tr>
<td></td>
<td>Aspart (Rs.650/- U-100)</td>
<td>Detemir (NA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucine (NA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA : not available; B : Bovine; P : Porcine
have a shorter duration of action after subcutaneous injection (Fig. 2). Amino acid substitutions (e.g. substitution of aspartic acid at B28 for proline) were selected as the best way of reducing the tendency of insulin molecules to aggregate in solution.
Longer-Acting Analogues (Glargine, Detemir)

The present intermediate- and long-acting insulin preparations are based on suspensions of insulin in crystalline or amorphous form, and they are all associated with large inter- and intra-subject variation in absorption and timing of effect. Furthermore, the duration of effective action is not sufficient to provide 24h basal insulin requirements with a single injection, and twice-daily injection leads to the possibility of in-between meal hypoglycemia, especially nocturnal hypoglycemia if a dose sufficient to control fasting plasma glucose is used. Therefore, a search was initiated for new insulins capable of producing a more reproducible and slower absorption without a tangible peak.

The initial idea was to change the isoelectric point of human insulin (pI 5.4) toward neutrality in order to obtain an insulin with low solubility at the pH of the tissue, i.e. an insulin, soluble in acid, that would precipitate and form a depot in the tissues after injection. Derivatives with extensions or substitutions at the B-chain termini, adding positive charges to the molecule, formed a depot after injection, and the protracted effect was shown to be more pronounced when the insulin derivative formed crystals at the injection site e.g. insulin glargine® (Markussen et al, 1987).

The newest concept for creating soluble, protracted-acting insulin has been the modification of insulin to promote its binding to existing serum proteins like albumin. The rationale of this approach is that such insulins will bind to albumin in the subcutaneous tissues and in plasma resulting in a reduced rate of absorption from subcutis and an increased plasma half-life relative to that of human insulin. A number of insulin derivatives with affinity for albumin were created by acylation of the ß-amino group of LysB29 with saturated fatty acids containing 10-16 carbon atoms. Maximal binding affinity was obtained for LysB29-tetradecanoyl des-(B30) insulin resulting in a longer duration of action, a flatter plasma insulin profile, and a lower inter-animal variability of response than NPH insulin. This compound called insulin detemir is currently in an advanced stage of clinical development.

However, the clinical development of long-acting analogues still showed that they may need to be given more than once-daily in real-time practice to many patients. This formed the rationale for the development of premix analogue equivalents. The premix analogue is a premixed insulin preparation that contains 30% rapid-acting insulin lyspro/aspart and 70% longer-acting analogue (protaminated insulin aspart/lyspro). It has been formulated to exploit the advantage of a rapid-acting insulin analogue lyspro/aspart (greater postprandial glycaemic control), in an injection regimen that is simple and convenient for patients. The protamine-crystallised component of lyspro/aspart mixture 30 has an extended duration of action like that of NPH insulin. lyspro/aspart mixture 30, however, contains no native human insulin molecules. The unprotaminated fraction of insulin aspart molecules is rapidly released from the injection depot into the blood, whereas the protamine-crystallised fraction has a protracted release. The longer-acting component, Protaminated insulin aspart, was developed as a component of Humalog NovoMix ® 30 and is not available as a stand-alone formulation.

Designer insulin makes early insulin initiation simpler and easier in type 2 diabetes. Treatment simplicity is an important issue in the initiation of insulin. Type 2 diabetes is a progressive disease in which insulin secretion, particularly in response to prandial stimuli, diminishes in the setting of insulin resistance. Initially, the resulting hyperglycaemia can be kept in check by dietary and lifestyle changes with or without oral hypoglycaemic agents (OADs), but ultimately exogenous insulin is required by many patients to keep blood glucose concentrations within acceptable limits. Evidence suggests that the prevalence of insulin usage in the diagnosed Type 2 diabetic population as a whole is about 30%, a prevalence which increases with duration of disease (ADA, 1996).

Many patients with Type 2 diabetes who require insulin to restore failing glycaemic control will have become used to treating their disease with simple regimens of oral medications. Their expectations may therefore be of continued simplicity of treatment. In addition, they may have lived with diabetes for many years without developing disabling complications, and it is unlikely that they will have
experienced ketosis. Therefore, they may not be particularly motivated to begin a demanding new treatment at such a ‘late stage’. Other patients starting insulin who have developed complications may be taking a potentially confusing array of medications. Many may be elderly. Under all of these circumstances, treatment simplicity is likely to be an important issue in the initiation of insulin.

Insulin analogues makes early insulin initiation simpler and easier: Insulin is usually initiated in Type 2 diabetes in simple regimens, once- or twice-daily, NPH insulin being a popular choice. However, this treatment provides poor control of the postprandial component of glycaemic dysregulation in Type 2 diabetes has provided the opportunity to address both the prandial and basal aspects of glucose regulation in insulin regimens that are simple to adhere to.

a. Combining Designer Insulin with OADs
Combining designer insulin with oral agents is commonly used in Type 2 diabetes as a means of facilitating the transition to insulin therapy, and of capitalising on remaining beta-cell function. Data show that can be used in combination with major classes of oral agents, including metformin, sulphonylureas, thiazolidinediones, and prandial glucose regulators. Studies suggest that early use of designe insulin in combination with oral agents can achieve clinically useful improvements in glycaemic control in patients failing on oral therapy alone.

b. Once-daily Designer Insulin Metformin Combination
Once a day designer insulin like Glargine can be initiated as ‘BIDS’ therapy with metformin. Similarly Premixed Analogues 30/70 or 50/50 can also be added.

c. Combination with Glitazones
Designer Insulin has been shown to be an effective treatment combination with glitazones in type 2 diabetic patients. Studies have shown that the combination of Designer Insulin and glitazones offers better glycaemic control than the combination of other OADs and glitazones. The efficacy and safety of combining Designer Insulin with Pioglitazone has been proven in a few trials.

d. Switching to Designer Insulin from other Insulin Regimens
Patients currently following a simple insulin regimen (e.g. NPH insulin alone or Human Mixture 30/70 or 50/50 alone) are likely to be switched to a Designer Insulin regimen in an attempt to reduce postprandial hyperglycaemia, because of a desire to eliminate the pre-meal injection interval with conventional human insulin, or because of advantages attached to delivery systems in which Designer Insulin is available. Patients currently on advanced insulin regimens (e.g. basal-bolus therapy) will generally be able to address these issues by changes in their existing regimen (e.g. adjustment of bolus and basal dose to correct postprandial hyperglycaemia; use of rapid-acting analogue such as insulin lyspro/aspart as bolus component). However, there may be situations in which patients following an advanced, and therefore complex, insulin regimen may find adherence easier with twice-daily or once daily Designer Insulin and therefore actually achieve improved control.

An important question for physicians considering making such therapy changes is whether dose adjustment will be necessary. Initially, patients injected insulin at a daily dose equivalent to their pre-trial regimen; although they could subsequently vary the total daily dose according to requirement, little dose adjustment was required in connection with the change of therapy. Importantly, although total insulin dose, and overall insulin exposure, remained similar as patients switched therapy, Designer Insulin resulted in earlier and greater insulin exposure in the immediate postprandial periods following breakfast and dinner in comparison with Human. A straight unit-for-unit transfer is therefore recommended when patients are initially switched from Human Mixture to Designer Insulin. However, it is important to remember that, as with any change of insulin therapy, monitoring of glycaemic control may indicate the need for subsequent dose adjustment.
f. Designer Insulin can be given post meal

Freedom from Meal-time Injection Constraints with Designer Insulin

Patients using soluble human insulin as the mealtime component of basal-bolus or premixed regimens are recommended to inject this component approximately 30 minutes before meals. This is because human insulin is relatively slowly absorbed from the injection depot, so an appropriate injection–meal interval is required in order to coordinate the peak of insulin availability with physiological need. In clinical practice, however, only a minority of patients (some 25%) actually comply with this advice about injection–meal intervals, and more than 60% employ injection–meal intervals of ≤ 15 minutes (Overmann et al, 1999).

Insulin Glargine (Lantus™)

Insulin glargine is a long-acting biosynthetic human insulin made by elongation of the C-terminal end of the insulin B chain by two arginine residues, as well as substitution of the A21 asparagine residue with glycine (A21Gly, B31Arg, B32Arg human insulin). These modifications led to a shift of the isoelectric point from pH 5.4 of human insulin to 6.7, making insulin glargine less soluble at physiological pH levels. After sc injection, insulin glargine precipitates in the sc tissues, which delays its absorption and prolongs its duration of action. However more pain at the injection site has been reported in all clinical trials of the drug. Also the use of a long-acting insulin analogue as the sole insulin replacement therapy in type 2 diabetes does not appear to have any rationale as it ignores the contribution of postprandial hyperglycemia to overall glycemic control. The acidic nature of the insulin also prevents it from mixing it with neutral insulin.

Insulin glargine has a greater affinity to the IGF-I receptor than human insulin. The observation of a progression of retinopathy in some patients with type 2 diabetes treated with insulin glargine raised concerns, partly because IGF-I has been implicated in the development of retinopathy (Smith et al, 1999). A review of the retinopathy data and the lack of optic disc swelling, which is the most common ocular side effect of treatment with IGF-I, led to the conclusion that this finding was probably not related to insulin glargine.

The binding of insulin analogues to the IGF1 receptor has also been of concern. Such binding may lead to increased mitogenesis, growth promotion and carcinogenicity compared to human insulin. Consequently, before initiation of long-term clinical studies, insulin analogs should be tested for these effects. In a comment to the above-mentioned results it was recommended that it would be safest to use analogs in which the receptor binding parts of the molecule are not altered and the mitogenic effect does not exceed that of human insulin. The relative receptor binding, metabolic and mitogenic activities of the various insulin analogues are shown in Table 2.

### Table 2: Receptor Binding, Metabolic and Mitogenic Potency of Insulin Analogues

<table>
<thead>
<tr>
<th></th>
<th>Insulin receptor affinity</th>
<th>Metabolic potency</th>
<th>IGF-1 receptor affinity</th>
<th>IGF-1R/IR affinity</th>
<th>Mitogenic potency (Saos/B10 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>B10 Asp</td>
<td>205 ± 20</td>
<td>207 ± 14</td>
<td>587 ± 50</td>
<td>2.9</td>
<td>975 ± 173</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>84 ± 6</td>
<td>82 ± 3</td>
<td>156 ± 16</td>
<td>0.9</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>92 ± 6</td>
<td>101 ± 2</td>
<td>81 ± 9</td>
<td>1.9</td>
<td>58 ± 22</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>86 ± 3</td>
<td>60 ± 3</td>
<td>641 ± 51</td>
<td>7.5</td>
<td>783 ± 13</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>~18 – 46</td>
<td>~ 27</td>
<td>16 ± 1</td>
<td>0.9</td>
<td>~ 11</td>
</tr>
</tbody>
</table>

Adapted from Kurtzhals P et al. Diabetes 2000;49:999
Oral and Inhaled Insulin

There is a lot of excitement about oral/inhaled use of insulin. Currently it is undergoing Phase II/III trials in North America and Europe. The inhaled insulin delivery devices are shown in Figure 3a, 3b, 3c and 3d. It is very similar to asthma inhaler. Preliminary data of Oral Insulin – Oralin with Pioglitazone is shown in the table and graphs below. It is relevant to note that drugs like Pioglitazone will be playing a vital role in making diabetics ‘Insulin Free’.
Conclusion

The aim of insulin replacement therapy is to normalize blood glucose in order to reduce the complications of diabetes. The pharmacokinetics of the traditional insulin preparations, however, do not match the profiles of physiological insulin secretion. The introduction of the rDNA technology 20 years ago opened new ways to create insulin analogs with altered properties. Fast-acting analogs are based on the idea that an insulin with less tendency to self-association than human insulin would be more readily absorbed into the systemic circulation. Protracted-acting analogs have been created to mimic the slow, steady rate of insulin secretion in the fasting state.

Insulin therapy is at an important turning point; conventional insulin treatment clearly has deficiencies which are being addressed by designing analogs to meet the challenge of bringing blood glucose into the normal range in order to minimize the complications of diabetes mellitus. Development of the monomeric insulin analogs represents a major landmark in the evolution of insulin treatment. However, there is still much to be done with regard to improving protracted insulin for basal supply.

Until recently, available insulin preparations for subcutaneous administration made it almost impossible to achieve good glycaemic control without substantial disruption to the patient’s life style. Recombinant DNA technology has made it possible to design insulins with improved pharmacokinetic and dynamic characteristics to better provide the prandial (bolus) and basal insulin needs. The pharmacokinetics of rapid acting and longer acting insulin analogues for subcutaneous administration helps to more accurately mimic physiological insulin dynamics of people without diabetes. However, to approximate normoglycaemia without causing hypoglycaemia, a logical approach to insulin therapy, tailored to the individual patient, is needed.

The standard preparation of insulin lyspro/aspart has the potential to better mimic the physiological response to meals than regular human insulin. Insulin lyspro/aspart when combined with a suitable basal insulin improved overall glycaemic control and led to a similar or lower number of hypoglycaemic episodes compared with a similar regular human insulin regimen. Both insulin lyspro/aspart and biphasic insulin lyspro/aspart provide for exible and convenient administration. Insulin aspart is now well established as an effective and convenient means of providing glycaemic control which offers clinical and practical advantages over regular human insulin.

If we consider the evolution of insulin therapy in India, introduction of newer insulins have always had a significant impact on patient care. In an order these have been the introduction of highly purified
insulin followed by that of human insulin and still later by insulin delivery devices. Insulin analogues are sure to impact patient care in a similar manner. Inhaled and oral insulin are just round the corner.

References