Chapter

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Premixed Insulin Analogues: Best of Both Worlds

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Insulin is not only required by patients diagnosed with type 1 diabetes mellitus, the majority of patients with type 2 diabetes mellitus also eventually require insulin[1]. Insulin is the most effective and safe therapy for diabetics, if taken properly. Initiation of insulin therapy poses considerable challenges for both patients and health care providers. Common patient concerns include anxiety about injections, the time needed to learn injection technique and fears of weight gain and hypoglycemia.

Many patients start insulin therapy using NPH insulin or another long acting insulin that only provides basal coverage. Optimal glycemic control usually is not achieved with long acting insulin alone; therefore it is necessary to use these in combination by administering multiple daily injections.

Basal bolus therapy with multiple daily injections or an insulin pump is the most physiological approach to insulin replacement therapy. Alternatively premixed insulins provide both basal and prandial coverage in one injection. They are suitable for starting insulin therapy in patients who desire a simple and convenient regimen and are not willing to administer or do not need basal bolus therapy.

Insulin analogues were developed to more closely mimic physiological endogenous insulin secretion. They have a more predictable onset and duration of action than human insulin formulations. The development and use of insulin analogues has also increased flexibility for dose administration and meal times. Rapid acting analogues can be administered just before meals to cover postprandial glucose excursions. While long acting analogues should be administered at convenient time once or twice daily.

Premixed insulin analogues, containing both rapid and intermediate acting components are usually administered twice daily with one injection at breakfast and dinner time. A recent study shows that a once daily injection at dinner time can be effective for many patients.

Furthermore, for patients not achieving optimal glycemic control with two injections, an additional injection can be added at lunch time[2]. Therefore, it may be appropriate to commence with one injection at dinner time (or the largest meal) and add additional injections as necessary. This can enable some patients to be managed with premixed insulin analogues throughout the course of their disease.

TREAT-TO-TARGET CONCEPT

Landmark studies have proved that strict glycemic control can minimize the risk of developing microvascular and macrovascular complications in patients with type 1 or type 2 diabetes[3-6]. American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF) recommend strict glycemic goals. The goals differ slightly (Table 1), with the AACE recommend treatment goals for HbA1c ($\leq$ 6.5%) and postprandial glucose (< 140 mg / dl) being more stringent than those of the ADA (< 7% and < 180 mg / dl respectively). Therefore treatment of diabetes should be directed to achieve this target glycemic control preventing the long-term complication of diabetes.

Table 1: Glycemic targets for diabetes management

	HbA1c	*Pre-prandial plasma glucose*	*Post-prandial plasma glucose*
ADA	< 7%	90-130 mg/dL	< 180 mg/dL
AACE	< 6.5%	< 110 mg/dL	< 140 mg/dL

IMPORTANCE OF POSTPRANDIAL HYPERGLYCEMIA

Numerous epidemiological studies confirm that controlling postprandial plasma glucose (PPG) is important for reducing morbidity and mortality associated with hyperglycemia[7,8]. In the DECODE (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe) study of > 25000 subjects, any increase in postprandial glucose resulted in a significant increase in mortality regardless of the level of fasting glucose[7]. In the Diabetes Intervention Study[8], patients with type 2 diabetes, who died during 11 years follow up, had significantly high postprandial blood glucose values at screening than those who completed follow up, despite comparable fasting plasma glucose at base line.

It has been suggested that postprandial hyperglycemic spike causes medio-intimal carotid thickening which is responsible for poor cardiovascular outcome[9]. Regression of carotid intima-media thickening occurred in 52% of type 2 diabetic patients treated with repaglinide, a prandial glucose regulator, compared with 18% treated with glyburide[10].

Evidence also suggest that overall glycemic control, as reflected by HbA1c, requires control of both basal and post prandial (PP) blood glucose levels. A study involving 290 patients with type 2 diabetes not responding to therapy with two oral anti-diabetic drugs (OADs), in patients with mild or moderate hyperglycemia, postprandial glucose excursion proved to be the predominant factor contributing to overall hyperglycemic status, whereas in patients with severe disease (HbA1c > 8.4%) the fasting glucose was the main contributor. This suggests that towards the achievement of glycemic target PPG had a greater role in glycemic control than fasting plasma glucose. Therefore, both fasting and PP should be considered in management of diabetes[11].

INITIATING INSULIN THERAPY

Endogenous insulin peaks within 15 to 45 min of beginning a meal and returns to baseline after 80-120 min of meal initiation. The goal of insulin therapy is to reproduce closely the pattern of endogenous insulin secretion that occurs in people without diabetes. This pattern includes two components i.e., basal insulin secretion taking care of glucose regulation in the liver, muscle, and adipose tissue, and postprandial spikes of insulin secretion taking care of postprandial glycemic spike. Strict glycemic control to achieve target requires optimization of both basal and postprandial coverage.

NEED OF PREMIX ANALOGUES

Psychological resistance to insulin may arise because of fear of injections along with concerns of weight gain, hypoglycemia and perceived adverse impact on life style. Premixed insulin contains varying portions of short or rapid acting and intermediate acting insulins. They have been developed in an attempt to meet the needs of patients who require both basal and prandial insulin therapy but wish to limit the number of injections.

The earliest premix insulin developed contained NPH insulin as basal component and regular human insulin as prandial component in ratio of 70:30. But longer time to peak action (1-5 hours) and long duration of action of the regular insulin component make it less ideal regimen. Also it has to be administered at least 30 min before the meal and delayed trough causes increased risk of hypoglycemia after a meal[23].

These pharmacokinetic and pharmacodynamic shortcomings of human insulin 70:30 have been overcome with the introduction of premixed insulin analogues containing a rapid acting analogue for PPG control and intermediate acting for basal glycemic control. It can be administered within 15 minutes of a meal, which increases convenience for patients with irregular meal schedules. Two premix insulin analogues formulation are currently available in the US, insulin lispro 75/25 and biphasic insulin aspart 70/30. An additional formulation of premixed insulin lispro 50/50, BIAsp 50/50 and BIAsp 30/70 is available in Europe[12].

EVIDENCES WITH PREMIX ANALOGUES

The efficacy of premix analogues has been assessed in a variety of clinical trials both open labeled and blinded. Trials generally had an active comparator arm of human insulin 70/30.

Pharmacokinetic Superiority

A study in type 2 diabetic patients insulin lispro 75/25 significantly reduced peak blood glucose concentration compared with human insulin 70/30 (–9%; $p < 0.05$) and NPH insulin (–32.7%; $p < 0.005$)[13].

In another study postprandial blood glucose excursion was significantly lower (–13%; $p < 0.001$) with insulin lispro 75/25 than human insulin 70/30[14]. In both the studies the area under the glucose concentration time curve was less in the insulin lispro 75/25 as compared to human insulin 70/30.

The pharmacokinetics and pharmacodynamics of BIAsp 70/30 have been studied in healthy individuals in two trials[15,16]. These trials used a randomized double blind crossover design with a comparator arm of Human insulin 70/30. They measured blood glucose profiles[15] or glucose infusion rates or blood insulin levels following a standard meal. In both the studies the time to peak insulin concentration was significantly faster (30–50%; $p < 0.0001$) with BIAsp 70/30 as compared to human insulin 70/30. Also, peak insulin concentration was 50 to 70% higher in the BIAsp 70/30 group. Compared with human insulin 70/30, treatment with BIAsp 70/30 necessitated a 37% increase in the glucose infusion rate during a euglycemic clamp procedure over the first 4 hours ($p < 0.0001$)[16]. This is attributed to the more monomeric structure of rapid acting component, insulin aspart, which imparts it with the ability to enter the circulation rapidly.

Better Glycemic Control

Herz et al[17] measured 24 hours plasma glucose profiles in patients with type 2 diabetes on 3 consecutive days. He compared insulin lispro 75/25 to human insulin 70/30 and injected those 5 min before the meal (breakfast and dinner). Post-meal glucose increment was significantly ($p = 0.018$) reduced more with insulin lispro (-32.6%) as compared to human insulin mix (-29.4%). The AUCglu between breakfast and dinner were also lower with lispro mix 75/25 ($p = 0.001$). In this study human insulin 70/30 was administered 5 min instead of 30 min before the meals. Because of its delayed onset of action it has not shown comparable glycemic control.

Matto et al[18] compared the efficacy of insulin lispro 75/25 and human insulin 70/30 in 151 type 2 diabetic patients during Ramadan. The patients during Ramadan usually consume two meals i.e., before sunrise and after sunset. Insulin lispro 75/25 and human insulin 70/30 were administered immediately and 30-40 min before the meal respectively. Mean 4-point blood glucose profile was significantly ($p=0.004$) lower with insulin lispro 75/25 than the patients treated with human insulin 70/30. Body weight did not change significantly in either group.

Similarly Roach et al[19] in another 6 month crossover study with two premix formulations found that treatment with a premixed analogue (lispro mix) formulation resulted in significantly lower postprandial blood glucose values as compared with premixed human insulin formulation ($p<0.05$). Both treatments achieved comparable overnight glycemic control with no significant difference in body weight.

Several studies have compared long term glycemic control with twice daily BIAsp 30 with either NPH or Human insulin 70/30 in the comparator arm[20-22]. In a randomized double blind trial by Christiansen et al[20] comparing 403 patients with type II diabetes, insufficiently controlled on OADs or NPH insulin. Patients were randomized to receive BIAsp 30 or NPH twice daily after stopping OADs for 16 weeks. This regimen resulted in comparable reduction in HbA1c (0.67% and 0.61%) respectively in the two arms. Postprandial glucose improved significantly with both treatments but the postprandial increment over the three meals was significantly lower in the BIAsp 30 arm as compared to NPH arm ($p<0.0001$). BIAsp 30 is an effective agent for both metabolic and postprandial blood glucose control and is particularly effective for patients treated with OADs/ once daily NPH.

Boehm et al[21] compared postprandial and overall glycemic control in a population of patients with type 1 or type 2 diabetes (n=294) treated with BIAsp 70/30 or human insulin 70/30 in a randomized, open label parallel group study. The study was initially planned for 12 weeks then serially extended for one, two and four years. Both types of insulin were administered twice daily, before breakfast and dinner. BIAsp 70/30 was administered immediately before the meal, while human insulin 70/30 was injected 30 minutes before the meal. While the reduction in HbA1c with either treatment was not statistically different, treatment with BIAsp 70/30 resulted in a more favorable degree of postprandial blood glucose control than human insulin 70/30. Analysis of the 8 point self monitored blood glucose profiles indicated that blood glucose values after breakfast, before lunch, after dinner and at bed time were also significantly lower with BIAsp 70/30. No weight gain occurred during the trial.

After completion of this 3 month trial the study patients with type 2 diabetes (n=125) were allowed to continue treatment in an open–label fashion for an additional 21 months[22]. There was no significant difference in HbA1c values between the two treatment groups. While body weight increased by 2 kg in patients

treated with human insulin 70/30, it only increased by 0.5 kg in patients treated with BIAsp 70/30 (p=0.07).

The efficacy of BIAsp 70/30 has also been compared with that of insulin lispro75/25 in an open label cross-over trial including 137 type 2 diabetic patients. They were randomized to receive either BIAsp 70/30 or insulin lispro 75/25 before breakfast and dinner for 12 weeks[23]. The HbA1c reduction was same i.e. 0.5% for both the groups. Similarly, the blood glucose profiles seen following both treatments were comparable. However, 74% of the patients preferred to continue using the BIAsp 70/30 pen device compared with the insulin lispro 75/25 pen (p<0.001).

The flexibility of timings BIAsp 70/30 injections in relation to meal times has also been investigated in the elderly[24]. In this 12 week open label, two arm crossover study, elderly patients with type 2 diabetes were randomized to receive BIAsp 70/30 twice daily, administered 5 min before or 15-20 min after the morning and evening meals. Glycemic control was assessed by HbA1c and post prandial glycemic control. Glycemic parameters were the same with either treatment. The study concluded that postprandial administration of BIAsp 70/30 can be used as a treatment option in elderly patients.

Lispro75/25 vs. BIAsp 70/30

In patients with type 2 diabetes postprandial glucose excursions over 5 hours after the meal with BIAsp 30 were 10% and 17% lower compared to the insulin lispro 75/25 and human insulin respectively. The AUC values of glucose excursions from baseline were lower after treatment with either BIAsp 30 or insulin lispro 75/25 than with human insulin 70/30 during the first five hours of postprandial period (p<0.001)[25].

THE RIGHT CHOICE FOR INSULIN INITIATION: PREMIX ANALOGUE VS BASAL ANALOGUE

As we all know that achieving stringent glycemic targets is the goal of current diabetic therapy. There is always a dilemma whether to start insulin naïve or OAD failure patient on premix or basal insulin. Obviously insulin providing better glycemic control will help in achieving targets blood glucose level at an earliest and reducing the incidence of diabetic complications. To figure out the best therapy few treat to target trials were done comparing premix analogue and basal analogue. We will look into two studies with lispro 75/25 and BIAsp 70/30 each, which shows that initiating therapy with premix analogue is much better as compared to basal analogue i.e. glargine.

Malone et al[26,27] conducted 32 week, open label crossover studies evaluating glycemic control in patients with type 2 diabetes treated for 16 weeks with either insulin lispro 75/25 before breakfast and dinner and insulin glargine, a basal analogue at bed time. One study examined insulin naïve cases and the other examined patients inadequately controlled on current antidiabetic therapy. After a 6 to 8 weeks run-in-period, patients were randomly assigned to one of the two treatment regimens. In both the studies the dosage of insulin lispro and glargine were titrated on the basis of fasting and postprandial blood glucose values The HbA1c reduction from the baseline was 1.3 and 0.9% for insulin naïve cases in lispro 75/25 and glargine respectively. Similarly HbA1c reduction was 1.0% vs. 0.42% for patients inadequately controlled on insulin in 75/25 and glargine respectively. A higher percentage of patients treated with lispro 75/25 and metformin has achieved the HbA1c target of < 7% as compared to glargine arm i.e. (42% vs. 18% in insulin-naïve patients; 30% vs. 12% in patients previously treated with insulin).

The efficacy of BIAsp 70/30 before breakfast and dinner has been compared with insulin glargine once daily in a 28-week study of insulin-naive patients with type 2 diabetes inadequately controlled on OADs[28]. In this randomized, open-label parallel group study, metformin was adjusted to 500 mg/ day before insulin therapy was initiated. One-third of the patients also used pioglitazone. Insulin was subsequently titrated to a target fasting blood glucose concentration of 80–110 mg/dl. After treatment, the patients who received BIAsp 70/30 had significantly lower values of HbA1c than patients receiving insulin glargine (6.9% vs. 7.4%; p < 0.01). More patients treated with BIAsp 70/30 (66%) achieved HbA1c target of < 7.0% in comparison to 40% in the glargine arm (Fig. 1). Both arms were having similar fasting plasma glucose control; however BIAsp 70/30 arm has 25% more reduction in post prandial increment than glargine arm. Weight gain was higher in patients using BIAsp 70/30 as compared to glargine arm.

ONCE DAILY ADMINISTRATION OF PREMIX ANALOGUES

Transitioning safely to insulin therapy when oral antidiabetic agents fail to provide adequate glycemic control is a critical aspect of care for the patient with type 2 diabetes mellitus (T2DM). Kilo et al[29] evaluated the clinical effectiveness of starting patients on a

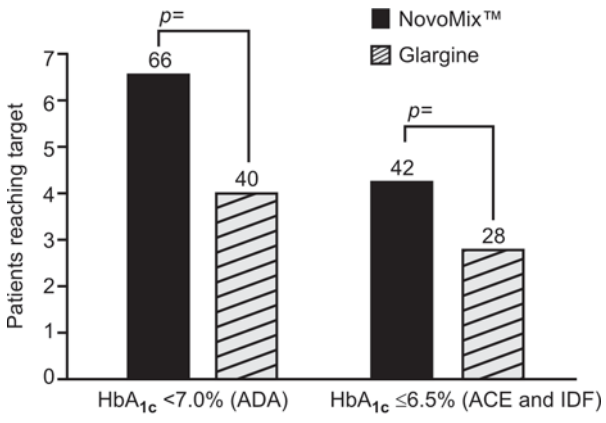

Fig. 1: Bar diagram achieving HbA1c targets in INITIATE study

relatively simple regimen of once-daily injections of either biphasic insulin aspart 70/30 (10 min before dinner), NPH insulin (at 10 p.m.), or biphasic human insulin 70/30 (30 min before dinner) in combination with metformin. All three treatment regimens were well tolerated. HbA1c decreased by 2.3%, 1.9% and 1.8% from base line after treatment with BIAsp 70/30, NPH insulin or human insulin 70/30 respectively. The results indicated that patients with T2DM can safely and effectively begin insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin.

Lund et al[30] at Steno Diabetic Center assessed the effect of once daily BIAsp 70/30 in combination with metformin or repaglinide in 86 non obese type 2 diabetic patients. Patients switched to 2 or 3 daily injections after 3, 6 or 9 months if target glycemic goals were not reached. After 3 months the majority (14% of all patients) who reached target HbA1c < 6.5% were treated with once daily BIAsp30 injection compared to only 10% of all patients after 12 months. He concluded that BIAsp30 in combination with OHA can be initiated once daily pre-dinner, but most non-obese patients need more than one daily injection after one year.

A 48 week treat to target, open label trial was conducted with BIAsp 70/30 in patients with type II diabetes not achieving glycemic targets with OAD treatment with or without basal insulin[2]. In 100 patients with a mean HBA1c of 8.6% at baseline, an HbA1c of < 7.0% was achieved by 765, including 39% using once daily administration before dinner. An HbA1c of < 6.5 % was achieved by 57% of patients, including 21% using once daily administration before dinner.

In a 4-month, parallel open-label study,[31] 172 patients who had been taking glyburide 15 mg/day were randomized to receive either insulin lispro 75/25 before breakfast and dinner (n = 85) or to continue glyburide 15 mg/day (n = 87). Glycemic control was assessed by HbA1c measurements and self-monitored blood glucose profiles. The HbA1c reduction was more with a slight increase in weight gain in lispro 75/25 as compared to glyburide arm.

HYPOGLYCEMIA WITH PREMIX ANALOGUE

Hypoglycemia is the major safety concern with insulin therapy. Because of mealtime administration, premix analogues have the potential to reduce hypoglycemic episodes particularly in patients who fails to take human premix 70/30 half an hour before the meals. Also, meal time flexibility will help children and elderly to adjust their insulin dosage according to the meal amount. A minor hypoglycemia is judged by classic signs and symptoms, and can be managed by the patient himself. However, patient needs to be assisted in case of major hypoglycemic episode. Normally trials were not planned keeping hypoglycemic episode as the primary end point.

Episodes of minor hypoglycemia with insulin lispro 75/25 and BIAsp 70/30 in comparison to human insulin 70/30 in separate trials were low and not statistically different. In a comparison of insulin lispro 75/25 and human insulin 70/30 in patients with type I and type II diabetes, two episode of major hypoglycemia was noted with lispro 75/25 in contrast to 4 cases with human insulin treatment[19]. Similarly according to long-term study of Boehm et al, (Fig. 2) the proportion of patients.

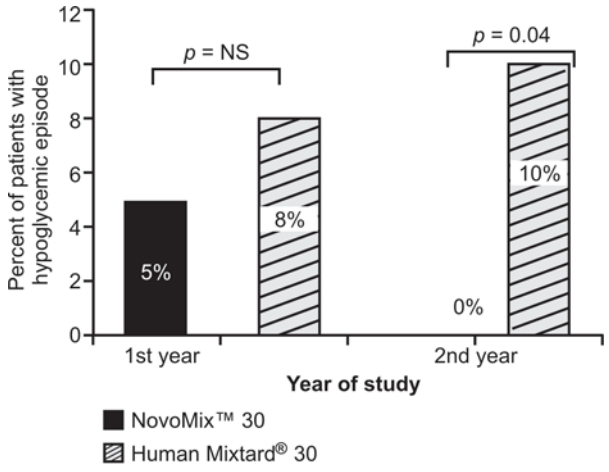

Fig. 2: Chart depicting major hypoglycemic episodes at the end of two year in Boehm study

Patient with at least one hypoglycemic episode experiencing major hypoglycemia was same in both BIAsp 70/30 and Human insulin 70/30 group but it was significantly lower with BIAsp30 than with BHI30 during the second year (BIAsp30, 0%; BHI30, 10%; P=0.04)[22].

PRACTICAL ISSUES IN USING PREMIXED ANALOGUES

As we all know that most physiological regimen for insulin replacement is basal bolus therapy or an insulin pump. For patients unwilling to use, or not needing, basal bolus therapy, a premixed insulin analogue regimen may be appropriate as it provide more effective postprandial and similar basal control of blood glucose levels as compared to human insulin 70/30. Hermansen have shown that postprandial increment was less in BIAsp 70/30 as compared to lispro 75/25.

Ideally the therapy should be targeted on patients who desire a convenient and simple insulin regimen, have HbA1c > 7% on maximal OAD therapy[3], have unwillingness to undertake more frequent blood glucose monitoring and carbohydrate counting, have routine life style and consistent meals. Premix analogues are usually administered twice a day at breakfast and dinner time. This provides sufficient insulin for meal time glucose excursions combined with the basal requirements of the body. Jain et al[2] has shown that patient can be started with once daily injection with dinner and can be intensified with twice or even thrice daily regimen with constant titration based on blood glucose levels. Thrice daily dosing is suitable for individuals having heavy lunch, the concept being more prevalent in India. Alternatively, a rapid acting secretagogue or insulin analogue can be added with twice daily premix analogue to cover lunch time glucose excursions.

The diabetic therapy has to be customized in individual patient taking care of hypoglycemic episodes and weight gain. Patient can be started with once daily premix analogue in combination with an OAD. In general, the combination of metformin and insulin appears to be beneficial in terms of achieving optimal glycemic control with minimal hypoglycemia and weight gain and lower insulin doses than would be needed with insulin alone. Starting with low dose of premix analogues minimizes the risk of hypoglycemia. Many trials have been discussed above () showing better results with combination of BIAsp 70/30 and Metformin.

Also three recent comparative randomized trials have shown that premix analogue twice daily in combination with metformin are more likely to reach glycemic target than those using insulin glargine in combination with metformin. This is because the premixed analogues take care both of fasting plasma glucose as well as meal time glucose excursions, while insulin glargine only provide basal coverage. Although the risk of minor hypoglycemia was more with premix analogues in two studies the risk can be reduced by less stringent titration schedule. Furthermore the hypoglycemic episodes occurred mainly during the day time. This suggests that common errors, such as meal skipping after insulin administration, may be responsible for hypoglycemia. Also Garber et al has shown that in-spite of intensification to twice and thrice daily regimen, the incidence of hypoglycemic episodes with BIAsp 70/30 has not increased.

Weight gain has not differed much either with premixed analogues or human insulin 70/30. Less weight gain in glargine arm as compared to premix analogues can be minimized by optimizing diet and exercise programs when commencing insulin therapy.

CONCLUSION

Premix analogues are effective and convenient agents that can be safely used for the management of blood glucose levels in patients with diabetes. They provide both meal time and basal insulin requirement. Also they are available in pen devices, which provide an easier, more accurate and less painful method for insulin delivery than vial and syringe. Since convenience, flexibility and quality of life influence treatment adherence, their availability and advantage should be explained to every patient.

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