Biphasic (Premix) Insulin Analogs in Type 2 Diabetes Mellitus

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Abstract: One of the causes of failure to achieve target HbA1C in type 2 diabetes mellitus is delay in starting insulin .The standard insulin fails in large number because soluble insulin used for postprandial glucose control does not have a fast enough onset of action ; it needs to be given 30 and 45 minutes before meals ,and has an inappropriately prolonged duration of action, while the longer-acting zinc formulations do not have the long duration of action required of a basal insulin , even with biphasic human insulin. Biphasic insulin analogs allows delivery of both basal and prandial insulin in 1 injection that can be administered closer to mealtime, and produce greater reductions in the magnitude of postprandial glucose excursions than biphasic human insulin with less incidence of major hypoglycemia. The data in this review discuss related recent patents and highlights the importance of biphasic insulin analogs in the management of type 2 diabetes mellitus.

Keywords: Type 2 diabetes mellitus, insulin analogs, glycaemic control.

INTRODUCTION

NATURAL HISTORY OF TYPE 2 DIABETES MELLITUS

The Diabetes Control and Complications Trial (DCCT) confirmed the relationship between diabetes control and the prevalence of chronic complications [1]. Based on this trial, the main goal of diabetes treatment is to obtain plasma glucose levels as close to normal as is currently possible with the lowest number of severe hypoglycemic episodes [2, 3].

The United Kingdom prospective diabetes study demonstrated the progressive decline in β-cell function that occurs over time in type 2 diabetes and the eventual need for insulin therapy in most patients [4]. Relatively large doses of insulin (≥1 unit/kg), compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance of type 2 diabetes and lower HbA1C to goal [5]. The National Health and Nutrition Examination Survey 1999-2000 showed that only 37% of adults with diabetes are achieving the target HbA1C level of <7% with the current medications [6]. One important reason for this is failure to appropriately initiate insulin therapy in a timely manner [7].

In individuals with normal glycaemic control, the beta cells produce enough basal insulin, even in the absence of food intake, to limit lipolysis and hepatic glucose output. During meals, a larger bolus of insulin is secreted to stimulate peripheral glucose uptake, which is secreted in two phases [8]. The first phase inhibits hepatic glucose production and the second phase stimulates glucose uptake. Patients with type 2 diabetes have a defect in the first phase of insulin secretion, which can lead to postprandial hyperglycemia .In order to achieve normal glycemia, therapy must be designed to parallel as closely as possible the pattern of endogenous insulin secretion in normal individuals [9].

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The daily physiological demand for insulin fluctuates and can be separated into two phases: (a) the absorptive phase requiring a pulse of insulin to dispose of the meal-related blood glucose surge, and (b) the post-absorptive phase requiring a sustained amount of insulin to regulate hepatic glucose output for maintaining optimal fasting blood glucose. Accordingly, effective therapy involves the combined use of two types of exogenous insulin: fast-acting meal time insulin and a long-acting basal insulin [9]. Therefore, the goal of insulin therapy is to mimic this basal-bolus pattern of endogenous insulin secretion to achieve near-physiological glycaemic control using a variety of available insulin formulations [10].

STANDARD INSULIN DRAWBACKS

Standard insulins consist of short- and long-acting preparations prepared by biotechnology, which are identical in sequence to human insulin. Regular insulin (e.g. Actrapid) has an onset of action between 30 and 40 min,with peak action at 2-3 hours, and an effective duration of 8-10 hours, which necessitates it to be injected 30-45 minutes before mealtime, and delayed onset of action fails to mimic physiological prandial insulin secretion [11, 12].

Longer-acting agents(delayed action insulins), such as insulatard or isophane (neutral protamine Hagedorn [NPH]), have an onset of action between 2 and 4 hours with peak action 4-10 hours and an effective duration of 12-18 hours [11,12]. NPH insulin preparations contain equal concentrations of insulin, zinc ions and protamine (highly basic protein) that cause insulin to crystallise at a neutral pH and was developed by Hagedorn and colleagues in 1946 [13]. Other delayed action insulins includes, Lente and ultralente preparations, which have a duration of action of 10-24 hours and 12-28 hours, respectively. These are amorphous or crystalline precipitates containing only a defined amount of zinc [13].

Despite modifications in the absorption characteristics and pharmacokinetic properties of insulin, these treatments still do not provide optimal timing of insulin action. For

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example, soluble insulin used for postprandial glucose control does not have a fast enough onset of action and has an inappropriately prolonged duration of action, while the longer-acting zinc formulations do not have the long duration of action required of a basal insulin. NPH has significant within-patient variability while the Lente and ultralente were discontinued by the manufacturer [14, 15].

Biphasic human insulin 30 ([BHI 30], 30% human insulin and 70% neutral protamine Hagedorn [NPH] insulin) are not ideal because of the limitations of the individual components [16] Fig. (**1**) and, needs to be administered at least 30 minutes before meals. To address these inadequacies, insulin analogs have been developed [13].

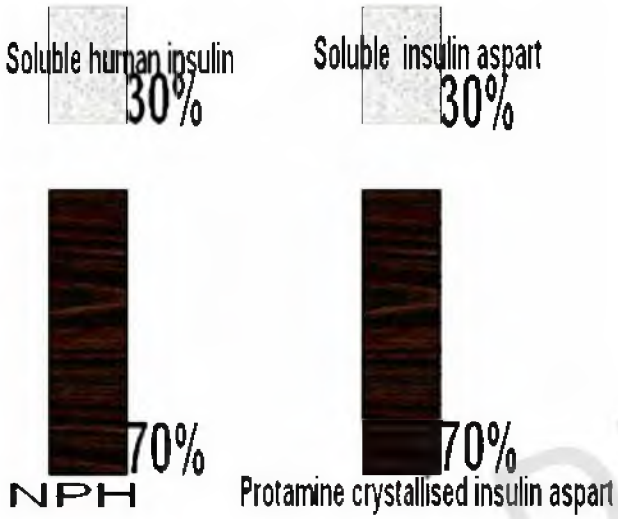

Fig. (1). Biphasic insulin (human and asprat).

ANALOGS (ANALOGUES) ERA

Insulin analogs are a group of insulin where the molecule of human insulin has been changed [17, 18]. The purpose of the molecular changes is to alter the *in vivo* properties of human insulin to obtain for instance a faster or slower action of the insulin.

Insulin has a natural tendency to associate into dimers and hexamers at high concentrations and neutral pH. Alterations in the insulin amino acid sequence to prevent self-association, such as those that promote charge repulsion and hydrophobicity changes, have resulted in insulins with a faster onset and shorter duration of action [19] .These insulins exist essentially as monomers, and are absorbed two to three times faster than soluble insulin. Conversely, changing the amino acid sequence to make insulin less soluble at physiological pH can delay its absorption and thus provide a more effective basal insulin supply.

ULTRA-RAPID ANALOGS

INSULIN LISPRO

This analog differs from human insulin by the inversion of the amino acid residues in positions 28 and 29 of chain B, proline–lysine in the case of human insulin, and lysine-proline for lispro insulin [20-22].

INSULIN ASPART

Insulin aspart (IAsp) is an analog of human insulin in which the amino acid proline, at position B28 on the insulin molecule, has been replaced by aspartic acid. This substitution results in a reduced tendency for self-association, thereby allowing a more rapid absorption from the subcutis. IAsp injected immediately before a meal therefore results in significantly reduced postprandial glucose levels compared with regular insulin.[18,21-24].

BIPHASIC (PREMIX) ANALOGS

A Biphasic insulin analog, addresses both the prandial and basal aspects of glucose regulation when used once or twice daily in patients with type 1 or type 2 diabetes [25]. They can be injected within 15 minutes of meal initiation, which is more convenient for patients with irregular meal schedules. They offer the advantage of being a more physiological treatment regimen, able to address prandial, as well as fasting, insulin requirements with one single injection, unlike basal insulins, which primarily address fasting glucose [26-30]. They are therefore the ideal, because postprandial glycaemic control on overall glycaemic control increases as HbAIC values get closer to the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommended HbAIC targets of <7% and ≤ 6.5%, respectively [31,32].

Biphasic insulin analogs allow delivery of both basal and prandial insulin in 1 injection and are more convenient than BHI 30 formulations [16]. They can be administered closer to mealtime, and produce greater reductions in the magnitude of postprandial glucose excursions than BHI 30 [16]. Advantages of biphasic analogs vs. BHI 30 are rapid onset of action of insulin, injection closer to mealtime and decreased postprandial hyperglycaemia [33,34] and 50% less incidence of major hypoglycemia [35].

There are two biphasic analogs in Europe now which are biphasic insulin aspart 30 (30% soluble and 70% protaminated insulin aspart; [BIAsp 30],Novomix 30) and biphasic insulin lispro(25% soluble and 75% protaminated insulin lispro 25 [Mix25], Humalog Mix25). The BIAsp 30 and Mix25, like the fast-acting analogs from which they are derived, also allow flexible injection timing, relative to meal timing, thus improving adherence, compliance and quality of life compared with premixed human insulin [25, 36].

PEN DEVICES

These new methods strive to maintain adequate glycaemic control while increasing patient compliance and satisfaction with insulin therapy [37].

Some of the disposable pens currently available include the FlexPen (Novo Nordisk, Nordisk A/S, 2880 Bagsvaerd, Denmark), Humalog Pen (Eli Lilly and Company, Indianapolis, Indiana, USA), and OptiSet Pen (Sanofi-Aventis;)

Pens offer the following advantages over vial and syringe: [37, 38]

i. They are more discreet.

ii. Patients are more accepting of this delivery system and therefore more readily comply with treatments.

iii. They are more convenient.

iv. They provide more accurate dosing.

v. They make injections easier and with faster injection times.

Patients generally preferred the FlexPen over the Humalog or the OptiSet Pen because it was perceived to be more convenient and easier to use [38].

CLINICAL STUDIES UNTIL NOW

Overall, the evidence suggests that biphasic analogs are cost effective and have useful advantages over BHI 30 for the treatment of type 2 diabetes [25, 39, 40].

Observational studies have demonstrated that they improved control of postprandial glucose is statistically associated with a significantly decreased risk of macro vascular [26-30] and microvascular [31] complications of diabetes.

One of the most well-studied biphasic insulins is BIAsp 30 [34].

Clinical trials evaluating the pharmacodynamics of BIAsp 30 in healthy individuals have shown that the fast onset of action seen with IAsp is retained in the biphasic formulation, whereas the duration of action has been extended to match that seen with BHI 30 [6, 9, 21, 36, 41-43].

To compare the efficacy and safety of BIAsp 30 with BHI 30 used in a twice-daily injection regimen in people with Type 1 and Type 2 diabetes Boehm, *et al.* find that post-prandial glycaemic control was significantly improved, without increasing the risk of hypoglycemia, and overall control was similar when people with Type 1 and Type 2 diabetes were treated on a twice-daily regimen with immediate premeal injections of BIAsp 30 compared with BHI 30 [35].

BIAsp 30 improves postprandial glycaemic control compared with both Mix25 and BHI 30 in subjects with type 2 diabetes in open-labeled, randomized,single-dose, three-way crossover trial of 61 insulin-treated subjects with type 2 diabetes who had no significant late diabetic complications [44] .

Patients with type 1 or 2 diabetes mellitus reported greater treatment satisfaction with insulin aspart or BIAsp 30 than with regular human insulin or BHI 30 [45].

Treat-to-target trials have shown that a goal HbA1C below 6.5 or 7% can be achieved with BIAsp 30. The risk of hypoglycemia is similar to or less than that seen with other biphasic insulins or NPH insulin [34] .

To compare the safety and efficacy of BIAsp 30 given twice daily with once-daily insulin glargine in patients with type 2 diabetes beginning insulin therapy and who did not use thiazolidinediones, which are contraindicated with insulin in the European Union Raskin *et al.* [29] found BIAsp 30 given twice daily in combination with metformin, was more effective than insulin glargine, given once daily in combination with metformin, at controlling blood glucose in insulin-naïve patients with type 2 diabetes, but was associated with increased weight gain and minor hypoglycaemic events.

Switching to a combination of BIAsp 30 with rosiglitazone was efficacious and well tolerated and provided an alternative to adding rosiglitazone to existing glibenclamide treatment in patients with type 2 diabetes mellitus whose metabolic control was inadequate with glibenclamide monotherapy [46].

BIAsp 30 with pioglitazone provided an efficacious and well-tolerated treatment alternative to glibenclamide plus pioglitazone or BIAsp 30alone in patients who previously were not well controlled on glibenclamide monotherapy or combination therapy [47].

In multicenter, randomized, open-label, parallel-group trial, insulin-naive patients with poorly controlled type 2 diabetes (HbA1C > or =8.0%) on OADs [48]. BIAsp 30 TID and BIAsp 30 BID plus metformin were associated with significantly greater reductions in HbA1C and postprandial plasma glucose compared with OADs alone.

In subjects with type 2 diabetes poorly controlled on OADs, initiating insulin therapy with twice-daily BIAsp 30 was more effective in achieving HbAIC targets than once-daily glargine, especially in subjects with HbAIC > 8.5% [16,29] and twice-daily BIAsp 30 plus metformin can reduce HbA1C and mean prandial plasma glucose increment to a greater extent than once-daily glargine plus glimepiride [49].

BIAsp 30 added to metformin could be an appropriate therapeutic option for achieving good glycaemic control, compared with the addition of a second OADs, particularly where HbAIC > or = 9% [50, 51].

Observational study in patients with type 2 diabetes failing OADs therapy with or without basal insulin was conducted to assess whether addition and self-titration of biphasic BIAsp 30 could achieve AACE /International Diabetes Federation (IDF) and ADA glycaemic targets (HbA1C< or =6.5 and <7%) initiation of once-daily BIAsp 30 to type 2 diabetes patients poorly controlled on various OADs regimens.It was an effective treatment approach for achieving glycaemic goals. Additional patients safely achieved these goals by increasing the number of BIAsp 30 injections from one to two, and then, if uncontrolled, from two to three doses per day. Eventually, most patients previously uncontrolled on OADs with or without basal insulin were controlled by the addition and vigorous titration of BIAsp 30 to oral agent therapy [52]. The same finding also seen by Tibaldi [53].

The glycaemic control of thrice daily treatment with BIAsp 30 without other antidiabetic therapy was tested in type 2 diabetic patients, in order to compare the glucose control of a 'high' mixture (BIAsp 70) or a 'medium' mixture (BIAsp 50) (70 or 50% soluble IAsp and 30 or 50% protamine-crystallized IAsp, respectively) administered just before dinner. To compare these regimens to conventional 30: 70 premixture on a BID basis.This study proved no significant differences [54].

In a study to compare the pharmacokinetics and pharmacodynamics of the BIAsp 30 with the equivalent BHI 30, administered twice daily, in patients with type 2 diabetes mellitus. Premeal injection of BIAsp 30 in a twice-daily regimen significantly reduced overall postprandial glucose excursions [43].

To show that a thrice daily meal-time BIAsp 30 treatment regimen is as efficacious as a 4 times daily basal-bolus regimen with NPH and insulin aspart (IAsp), Ligthelm *et al.* found a thrice daily meal-time BIAsp 30 regimen is a suitable alternative to an intensified insulin regimen in people with inadequately controlled type 2 diabetes mellitus, and requires fewer daily injections than a basal-bolus therapy without compromising efficacy and safety [55].

The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix 30 Therapy (PRESENT) study aims to assess the safety and efficacy of BIAsp 30 in patients with type 2 diabetes mellitus in routine clinical practice. It was a multiethnic observational study involving 21,977 patients from 13 countries (India, Iraq, Jordan, Kuwait, Lebanon, Qatar, Romania, Russia, Saudi Arabia, South Africa, South Korea, Turkey and the United Arab Emirates).They found that the use of BIAsp 30 monotherapy or in combination with OADs in clinical practice was effective and safe in patients with poorly controlled type 2 diabetes mellitus [56].

In a randomized multinational, multicenter, open-label, 2-period, crossover study, comparison of the efficacy and safety profiles of BIAsp 30 and Mix25 used in a BID injection regimen in patients with type 2 diabetes mellitus and to assess patients' preference for pen device (The NovoMix 30 FlexPen /NovoLog Mix 70/30 FlexPen [FlexPen] versus the Humalog Mix25 Pen/Humalog Mix75/25 Pen[Humalog Pen]) .Glycaemic control with BIAsp 30 and Mix 25 was found to be comparable in these patients with type 2 diabetes mellitus with similar safety profiles for both regimens. Patients preferred and experienced fewer problems with the FlexPen than the Humalog Pen [57].

Treatment with a twice-daily Mix25plus metformin, which targets both post-prandial and pre-meal blood glucose, provided clinically significant improvements in HbA1C, significantly reduced post-prandial blood glucose after each meal, and reduced nocturnal hypoglycemia as compared with once-daily glargine plus metformin, a treatment that targets fasting blood glucose [58].

WHAT ARE THE NEW PATENTS IN THE FIELD?

Biphasic Glucagons-Like Peptide 1(GLP-1) and Insulin

When OADs fail, the only current alternative is to treat patients with insulin that must be dosed and timed with respect to meal-related glucose excursions and hepatic glucose output during periods of fasting so as to effectively normalize glucose while reducing the risk of hypoglycemia. Control of the absorptive phase involving disposal of the meal-related blood glucose surge can be effectively achieved with commercially available regular insulin and monomeric insulin analogs. However, control of the absorptive phase involving disposal of hepatic glucose output during periods of fasting, especially between meals and during the bedtime hours, is not as effectively achieved with these insulins [59].

GLP-1 have a variety of physiologically significant activities.It has been shown to stimulate insulin release, lower glucagon secretion, inhibit gastric emptying, enhance glucose utilization preserve beta cells, inhibit beta cell apoptosis, and induce beta cell proliferation [60, 61]. Biphasic mixtures comprise a GLP-1 solid phase and an insulin solution phase is seems promising [59].

The present invention encompasses various biphasic mixtures comprising a GLP-1 compound in a solid phase and insulin in a solution phase. Preferably insulins include regular human insulin or a monomeric insulin analog [59]. The GLP-1 solid phase comprises an insoluble GLP-1 precipitate or crystal. The insoluble GLP-1 provides for a slowed absorption rate resulting in GLP-1 with a protracted action that is useful to control disposal of hepatic glucose output during periods of fasting, especially between meals and during the bedtime hours, as well as meal-related blood glucose surges. The insulin solution phase comprises insulin that can control disposal of the meal-related blood glucose surge, especially after the first meal of the day where glucose levels are potentially the highest.

CURRENT & FUTURE DEVELOPMENTS

Premixed insulins offer the advantage of being a more physiological treatment regimen, able to address prandial, as well as fasting, insulin requirements with one single injection and can be administered closer to mealtime. Unlike basal insulins, which primarily address fasting glucose. Future directions will be to incorporate insulin analogs with GLP-1 for better disposal of hepatic glucose output during periods of fasting, especially between meals and during the bedtime hours, as well as meal-related blood glucose surges.

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