The Switch Study: Switching from BHI 30 Novolet® to BIAsp 30 Flexpen®: 'Clinical Observations from the Netherlands'. Treatment Satisfaction when Switching from BHI 30 NovoLet® to BIAsp 30 FlexPen®

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Abstract

Aim: An open label non-randomized observational study was performed to observe and investigate the process of switching from premixed human insulin 30/70 (BHI 30) in NovoLet® to biphasic insulin aspart 30/70 (BIAsp 30) in FlexPen® in an outpatient setting; in terms of insulin dose, efficacy, hypoglycemic episodes, quality of life (WHO-5) and treatment satisfaction (ITSQ; Insulin Treatment Satisfaction Questionnaire).

Methods: Type 2 diabetic patients (aged ≥ 18 yrs) treated with BHI30 in NovoLet® who were switched to BIAsp 30 in FlexPen® were included in an open-labeled, multicenter, non-randomized, observational study. At baseline and 8 ± 2 weeks after switching to BIAsp 30 FlexPen® HbA^{1c}, insulin dose, number of hypoglycemic events and quality of life were measured.

Results: A total of 196 patients (54.3% female, aged 64.8 ± 12 years) with type 2 diabetes completed the study. Total insulin dose remained stable 52.8 ± 24.9 units at baseline vs. 52.0 ± 25.6 units after 8 weeks of treatment, as did HbA1c, 7.7 ± 1.4% at baseline vs. 7.7% ± 1.4%. No weight change was reported (81.6 ± 16.6 kg vs. 81.5 ± 16.7 kg). With BIAsp 30, a significantly lower number of total hypoglycemic episodes were reported (127 compared to 188 with BHI 30, $p < 0.001$). Significance remained for the subclasses separately (daytime 142 vs. 98, $p = 0.005$; and nocturnal 46 vs. 29, $p = 0.05$).

ITSQ results confirmed these findings: total score on 'hypoglycemic' subscale improved significantly from 78 ± 16.8 to 83 ± 16.0 ($p = 0.009$). The overall score improved significantly from 82.2 ± 14.6 to 85.5 ± 13.9 ($p = 0.036$). 85% percent of the patients were satisfied with the FlexPen® device and 89.1% wanted to continue treatment with FlexPen®. The WHO-5 scores after the final visit showed no general quality of life problems with average scores between 2.7 and 3.3.

Conclusion: The results of this study provided evidence that switching from BHI 30 NovoLet® to BIAsp 30 FlexPen® can be done easily on a unit by unit basis in daily practice in type 2 diabetic patients. After 8 weeks of treatment with BIAsp 30 there was a significant decrease in hypoglycemic episodes accompanied by a significant increase in treatment satisfaction.

Keywords: BIAsp 30, BHI 30, hypoglycemia, ITSQ, quality of life

Introduction

Patients with Type 2 Diabetes Mellitus who need insulin therapy are often treated with two injections per day, although a basal/bolus regimen is more physiologic. However in some people multiple-injection regimens may not be desirable. Their basal insulin secretion is often "normal" or even high due to insulin resistance and many patients are used eating small meals with snacks in between. In addition, many patients would find it difficult to maintain a four times daily regimen. Premixed insulin formulations with 30% short-acting and 70% long acting insulin are a practical option (Bebakar et al. 2007; Guisasola et al. 2008; Unger, 2008). Optimizing these regimens and promoting patient compliance will be of ongoing clinical importance.

Due to the delayed absorption as a consequence of dimerisation and hexamerisation of soluble human insulin(BHI 30, Mixtard 30®) in the subcutaneous tissue depot, the medication has to be administered

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30 minutes before mealtimes (Boehm et al. 2002) in order to reach adequate plasma insulin concentrations during a meal. Clinical experience and studies show that this advice is not followed by approximately two thirds of the patients who administer their insulin immediately before a meal for reasons of convenience and fear of premeal hypoglycemia (Boehm et al. 2004; Kapitza et al. 2004).

Biphasic insulin aspart 30 (BIAsp 30, NovoMix® 30) is a premixed insulin formulation containing 30% soluble insulin aspart and 70% protamine co-crystallized insulin aspart. Soluble insulin aspart is a human insulin analogue designed to remove the restrictions of the soluble human insulin therapy and having a lower tendency to form dimers and hexamers. The molecular structure is identical to that of human insulin, except for the substitution of proline by aspartic acid at position B28 in the B chain. This provides more rapid absorption following subcutaneous injection, a faster onset and shorter duration of action and therefore mimics the physiologic postprandial insulin response (Fig. 1) (McSorley et al. 2002), thus providing significantly reduced postprandial glucose excursions (Garber, 2005; Garber et al. 2007; Gough et al. 2007). Due to this rapid absorption it is possible to administer BIAsp 30 ten minutes before or even directly after a meal, which is particularly helpful when there is uncertainty about the quantity of food that the patient will eat during a meal.

BIAsp 30 is available in FlexPen®, a disposable pre-filled insulin injection device which is practical for many elderly diabetic patients as well as for diabetic patients with busy, active and mobile lifestyles (Rubin et al. 2004; Summers et al. 2004; Korytkowski et al. 2005; Meneilly, 2007).

Since administration convenience may improve patient compliance and treatment satisfaction, patients were switched from BHI 30 in NovoLet® to BIAsp 30 in FlexPen® in an open label, multicenter, non-randomized observational study. Furthermore this provided the opportunity to compare treatment with premix-insulin analogue to premix soluble human insulin. Observations were made in terms of dose ratio, efficacy, reported hypoglycemic episodes and patient treatment satisfaction during the eight week study period.

Methods

Patients with type 2 diabetes aged 31–94 years were included from five centers in the Netherlands: Rotterdam, Zwijndrecht, The Hague, Nijmegen and Zwolle. These patients, who were treated with BHI 30 in NovoLet®, were switched to BIAsp 30 in FlexPen®. Patients were ambulatory and capable of administering their own insulin. Selection was made at the discretion by the participating physicians from their daily practice during the enrolment period June 2006 till February 2007.

Data were collected at the start of the study (baseline) and at 8 ± 2 weeks after the start

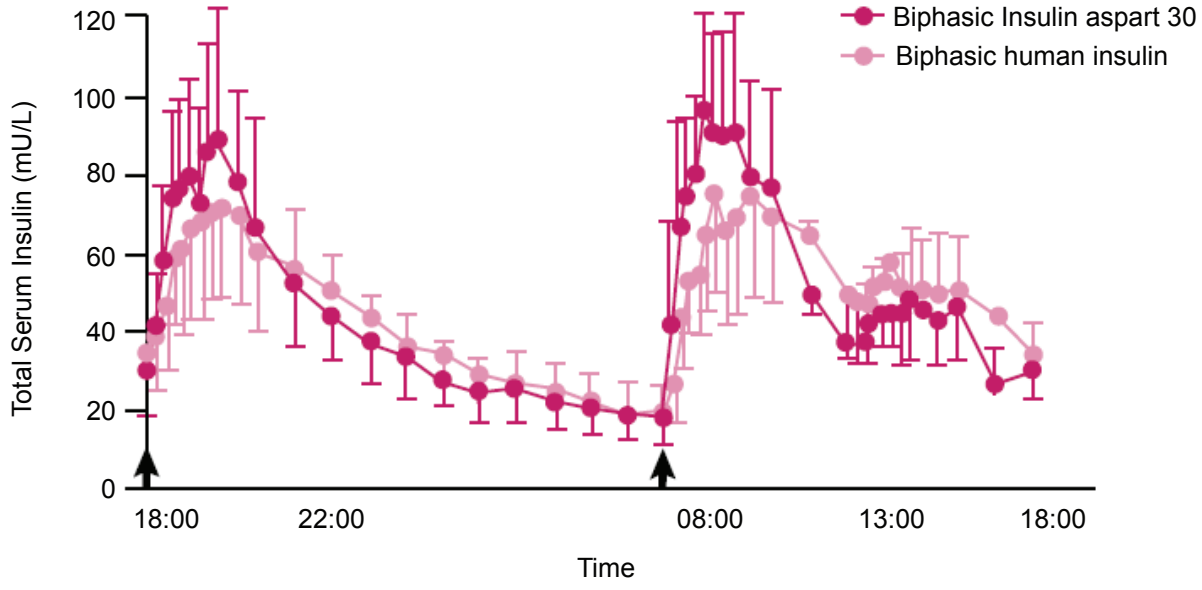

Figure 1. Profiles of biphasic insulin aspart 30 and soluble human insulin. Arrows indicate insulin injection (McSorley et al. 2002).

of BIAsp 30 FlexPen® (final visit). Since this is an observational study no extra measurements or interventions were done in order to avoid a study bias.

The switch from BHI 30 to BIAsp 30 was performed on a unit by unit base. Subsequently, if necessary, doses were adjusted according to blood glucose measurements. Patients were made familiar with specific use of the FlexPen® and received instructions concerning the injection time. Patients who used to eat snacks between meals in order to avoid hypoglycemia were told that this was not necessary during treatment with BIAsp 30; however no other dietary advice was given. Oral blood glucose lowering drugs were continued during the study protocol if prescribed.

Hypoglycemia

Patients were asked to report all hypoglycemic episodes occurring in the four weeks prior to the baseline and the final visits. Hypoglycemic episodes were divided into two categories: daytime and nocturnal and no specific time categories were made. Nocturnal hypoglycemic events were defined as events that occurred while the subject was asleep until getting up in the morning (before morning determination of FBG and morning injection). These categories were divided into two subclasses: minor and major hypoglycemic events. Minor hypoglycemic events were defined as events with one of the following characteristics: symptoms of hypoglycemia that resolved with oral carbohydrate intake or any asymptomatic blood glucose concentration <50 mg/dl (2.8 mmol/l). Major hypoglycemic events were defined as events with central nervous system symptoms and blood glucose <50 mg/dl. that resolved with carbohydrate intake.

ITSQ, Device Handling questionnaire, WHO-5

In order to measure patient satisfaction three questionnaires were used; the validated Insulin Treatment Satisfaction Questionnaire (ITSQ), a validated questionnaire consisting of 5 main topics and a total of 22 questions. A Device Handling Questionnaire, specifically designed to evaluate the use of the FlexPen® including simple straightforward questions like how convenient do you find the use of FlexPen®? And furthermore the Well Being index (WHO-5) (Anderson et al. 2004; Weaver et al. 1997). Patients were asked to fill in the Insulin Treatment Satisfaction Questionnaires (ITSQ) at the baseline visit and final visit whereas Device Handling Questionnaire and Quality of Life (WHO-5 well-being index) were filled in at the final visit only.

Statistical analysis

Analyses were performed based on the All Subjects Treated group, consisting of all subjects with type 2 diabetes who received treatment with BIAsp 30 FlexPen®.

All variables were listed and summarized using descriptive statistics (mean, standard deviation, median, range) for continuous variables and number and percentage for categorical variables. Ordered categorical variables were treated as continuous variables when calculating summary statistics.

The process of switching was evaluated by comparing the BIAsp 30 dosage, HbA_{1c} values and number of hypoglycemic events after 8 weeks of treatment with baseline values. The differences were summarized using descriptive statistics. A t-test was used to determine whether the change in HbA1c from baseline was statistically significant and a Fisher exact test was used to test whether the differences between visits were statistically significant for hypoglycemic episodes. Satisfaction was measured using the ITSQ, a questionnaire consisting of 22 items, evaluating satisfaction on a scale from 1 to 7. The ITSQ items were summarized using descriptive statistics (mean, standard deviation, median). A two-sided t-test (alpha = 0.05) was used to assess changes in the patients' satisfaction. Device handling was assessed by 7 questions on the use of FlexPen®, summarized using descriptive statistics. Quality of life was assessed using the "WHO-5 well being index". Each of the 5 items as well as the overall score were summarized using descriptive statistics.

This 8-week, multicenter open-label, non-randomized observational study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (WMA, 1997).

Results

206 patients with type 2 diabetes were enrolled in the study; 5 patients were excluded due to insufficient data during baseline or final visit, another 5 patients dropped out for personal or logistic reasons, such as dispensing BHI 30 instead

of BIAsp 30 by pharmacists or not starting on BIAsp 30 because one still had BHI 30 in stock. A total of 196 patients with type 2 diabetes completed the eight week multicenter open label protocol. Data is presented as mean ± standard deviation. Baseline characteristics of the patients is presented in Table 1.

Insulin dose

Total insulin dose remained stable between baseline and final visit, 53 ± 25 IU vs. 52 ± 26 IU.

Blood glucose control, HbA_{1c} and weight change

A slight but not statistically significant elevation of fasting blood glucose (FBG) was observed at the final visit (7.51 mmol/l at baseline vs. 7.93 mmol/l at 8 ± 2 weeks). Insufficient measurements were available to obtain a 24 hour blood glucose profile. After 8 weeks of treatment with BIAsp 30, HbA_{1c} did not change 7.8% ± 1.4 at baseline vs. 7.7% ± 1.5 at final visit (p = 0.99). No weight gain was reported 81.6 ± 16.55 kg at baseline and 81.5 ± 16.73 kg at final visit (p = 0.097).

Hypoglycemia

With BIAsp 30, a significantly lower number of total hypoglycemic episodes were reported, a 127 compared to 188 with BHI 30, $p < 0.001$. Significance remained for the subclasses separately (daytime 142 vs. 98, p = 0.005; and nocturnal 46 vs. 29, p = 0.05, Table 2).

Table 1. Baseline characteristics.

Number	196
Age (years)	65 ± 12
Sex M/F (%)	46/54
BMI (kg/m2)	29 ± 7
HbA_{1c} (%)	7,8 ± 1,4
Dose (IU)	53 ± 25
Duration of Diabetes (years)	14 ± 7,8
Ethnicity (%)	
Caucasian	73
Other	27
Oral blood glucose lowering drugs (%)	
Metformine	42.8
Glibenclamide	2
Rosiglitazon	0.5

Insulin treatment satisfaction questionnaire, ITSQ

The total score on the +'glycemic control' subscale did not change, (78.0 at baseline and 80.0 at 8 ± 2 weeks, p = 0.80). The total score on the 'hypoglycemic' subscale improved significantly from 78.0 ± 16.8 to 83.0 ± 16.0 (p = 0.009). The overall treatment satisfaction (ITSQ) score improved significantly from 82.2 ± 14.6 to 85.5 ± 13.9 (p = 0.036).

Device handling questionnaire

85% of the patients questioned were more than satisfied with the FlexPen® device than with NovoLet®. 89.1% of the patients wanted to continue their treatment with the FlexPen®.

Quality of life questionnaire (WHO- 5 well being index)

The WHO-5 scores at the final visit showed no general Quality of Life problems, with average scores ranging between 2.7 and 3.3 on a scale from 0–5.

Discussion

This open label non-randomized observational study was performed to evaluate the process of switching from premixed human insulin 30/70 in NovoLet® to biphasic insulin aspart 30/70 in FlexPen® in an outpatient setting in terms of

Table 2. Hypoglycemic events.

		Baseline	Final visit	
		BHI 30	BIAsp 30	P-values[1]
Daytime		142	98	0.005
	Minor	137	91	0.002
	Major	5	7	ns[2]
Nocturnal		46	29	0.05
	Minor	40	25	ns[2]
	Major	6	4	ns[2]
Total		188	127	<0.001

[1]P-values are based on a Chi-square test for one-way tables.
[2]No significance.

insulin dose, efficacy, hypoglycemic episodes, quality of life (WHO-5) , treatment satisfaction (ITSQ) and device handling. The results of this study support a unit by unit transfer from BHI 30 to BIAsp 30 resulting in unchanged HbA1c with an advantage of fewer hypoglycemic episodes.

Although 8 weeks of treatment is a rather short study period to draw strong conclusions about HbA1c measurements, BIAsp 30 appears to be at least as effective as BHI 30 in glycemic control when measured with HbA1c. This observation is consistently supported with the findings of other clinical trials.(Boehm et al. 2002; Garber, 2005; Gough et al. 2007). The data showed an overall significant reduction in hypoglycemic events without the need of changing the insulin dose. In patients where a further improvement in glycemic control (HbA1c) is desired, adjusting the total insulin dosage should be done according to blood glucose profiles.

Bearing in mind the profiles of BHI 30 and BIAsp 30 (Fig. 1) one might be concerned that there would be an increase of hypoglycemic events after breakfast, since this is not the largest meal of the day and therefore the short and rapid peak of insulin would induce postprandial hypoglycemic events. There was a slight but not significant increase in the number of major hypoglycemic events during the daytime but there were no specifications made about the circumstances surrounding these major daytime events. A possible explanation is that these patients injected their insulin and then waited longer than necessary with the BIAsp 30 having been used to BHI 30.

Our data revealed a significant reduction in the total of hypoglycemic events during daytime as well as at night. This reduction may be partly explained by a slight but not significant elevation of the fasting blood glucose after 8 weeks of treatment with BIAsp 30. This reduction in hypoglycemic events was confirmed in the ITSQ score where patients reported a significant improvement in hypoglycemic control. Realizing that scoring patients' satisfaction is a subjective endpoint, the results of the questionnaire and hypoglycemic event rate showed a similar improvement on hypoglycemic control after 8 weeks of treatment with BIAsp 30.

Overall results of the ITSQ and the device handling questionnaire show an improved satisfaction of the type 2 diabetic patients in both their insulin treatment as well as their device handling, hopefully resulting in better treatment compliance.

In conclusion, switching BHI 30 NovoLet® to BIAsp 30 FlexPen® can be done easily on a unit by unit basis in daily practice, in a population of type 2 diabetes patients resulting in stable glycemic control. After 8 weeks of treatment with BIAsp 30 no weight gain was reported. There was a significant decrease in hypoglycemic episodes combined with a significant increase in treatment satisfaction.

Competing Interests

N.M. Appelman-Dijkstra has received lecture fee from Novo Nordisk B.V.

This study was performed on the initiative of Dr. P.H.L.M. Geelhoed-Duijvestijn. She was involved in several previous studies initiated by Novo Nordisk B.V.

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Disclosure

The authors report no conflicts of interest.

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