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Original Article

Biphasic insulin aspart vs. human insulin in adolescents with type 1 diabetes on multiple daily insulin injections

Mortensen H, Kocova M, Teng LY, Keiding J, Bruckner I, Philotheou A. Biphasic insulin aspart vs. human insulin in adolescents with type 1 diabetes on multiple daily insulin injections
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Abstract: The aim was to compare clinical efficacy and safety of two treatment regimens: biphasic insulin aspart (BIAsp) injected at all three meals plus neutral protamine Hagedorn (NPH) insulin at bedtime vs. a human insulin regimen, premixed human insulin at breakfast and soluble insulin at lunch and dinner and NPH at bedtime. A total of 167 adolescents (80 males and 87 females) with type 1 diabetes was included in the trial (multinational, randomized, open-label, and parallel group). Each subject received either of two treatment regimens for a 4-month period. BIAsp was injected immediately before main meals, human insulin products 30 min before meals, and NPH at night. Glycemic control was monitored by eight-point evaluations (after 6 and 16 wks) and hemoglobin A1c (HbA1c) (after 2, 6, and 16 wks). Safety evaluations included adverse events and incidence of hypoglycemic episodes. HbA1c (mean ± SD) after 4 months on BIAsp (9.39 ± 0.14) was not significantly different from that with human insulin (9.30 ± 0.15). The average postprandial glucose increment in the BIAsp group was about half the increment in the human insulin group; the difference not statistically significant. The body mass index (BMI) increased in both groups, but significantly ($p = 0.005$) less in the BIAsp group. However, in males on BIAsp, the BMI decreased compared with those on human insulin ($p = 0.007$). No significant group differences were found for the rate of hypoglycemic episodes. We concluded that the BIAsp regimen was associated with similar glycemic control and similar incidence of hypoglycemic episodes as human insulin. However, the BIAsp regimen caused a significantly smaller increase in BMI, particularly in males, compared with the human insulin regimen.

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Key words: adolescents – biphasic insulin aspart – body mass index – prandial blood glucose – type 1 diabetes

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A well-structured insulin regimen should aim at controlling the current glycemic status of the disease in order to delay the progression of diabetes and reduce complications. Children with type 1 diabetes are commonly treated with short-acting insulins before main meals and with intermediate-acting insulins once or twice daily to cover basal insulin needs (1). To optimize blood glucose control and minimize the risk of hypoglycemia, it was found that the treatment schedule should be well balanced, particularly in children and adolescents whose lifestyle often includes frequent, vigorous exercise and frequent snacking. Furthermore, insulin therapy should be adapted to cope with rapid growth and hormonal changes, and the treatment should be able to overcome the increasing insulin resistance often observed during adolescence, especially in girls (2, 3). This paper presents comparative data in children and adolescents with type 1 diabetes offered either a standard treatment with short-acting plus long-acting human insulin or a treatment with a new biphasic formulation of insulin aspart (IAsp).

IAsp is a rapid-acting insulin analog with superior pharmacokinetic properties compared with those of human insulin. Trials with children and adolescents have indicated that the pharmacokinetic findings in these age groups are in accordance with those obtained in adults (4) and indicate that multiple daily treatments with biphasic IAsp (BIAsp) 30 might improve long-term glycemic control (5).

The aim of the present trial was to compare the efficacy and safety of BIAsp with premixed human insulin in adolescents on multiple daily insulin injections.

Methods

Population and procedures

The study involved 12 centers in eight countries in Europe and South Africa. Adolescents (10–17 yrs of age, puberty status $\geq$2 on the Tanner scale) (6) who had diabetes for at least 18 months were recruited. Subjects with poor compliance or poor glycemic control (HbA1c >13%) or with linguistic and/or social difficulties were excluded from the trial. Written informed consent was obtained from all subjects and their parents/legal representatives. One hundred and sixty-seven adolescents were included in this trial. Protocols, including laboratory procedures, were approved by the Ethics Committees in all countries for all sites, and all trial procedures were carried out in accordance with the Declaration of Helsinki.

Treatment and trial design

This was a multinational, randomized, open-label, parallel-group trial. After a short run-in period, subjects were randomized into one of two treatment groups. Treatment consisted (as a minimum) of three daily insulin injections before the main meals. One treatment arm (BIAsp group) received BIAsp 30, a mixture consisting of 30% rapid-acting, soluble IAsp and 70% long-acting, protamine-bound IAsp immediately before the meals; the other arm (human insulin group) received human insulin 30 min before the meal – usually before lunch and dinner – and premixed biphasic human insulin 30 [a biphasic mixture of 30% soluble human insulin and 70% long-acting neutral protamine Hagedorn (NPH) insulin] usually before breakfast. It has previously been shown that IAsp or BIAsp 30 taken just before or immediately after a meal is equally efficient as premixed human insulin taken 30 min before the meal in controlling postprandial blood glucose excursions (7–9). The adolescents were allowed additional insulin with snacks or at bedtime, if judged necessary by the investigator. Snack insulin was IAsp in the BIAsp group and rapid-acting human insulin in the human insulin group, while bedtime insulin was NPH insulin in both groups. The trial started with a screening visit 3–14 d before randomization (baseline), and randomization was followed by a 2-wk titration period (see Fig. 1). During the 16-wk treatment period following randomization, the subjects visited the clinic four times at regular intervals. The dose of insulin at screening was used as the starting dose in both groups. At trial entry, the majority of subjects were on a basal/bolus regimen (NPH was the most frequently used basal component). Forty-five were on a twice-daily treatment with biphasic insulin. Forty-six used rapid-acting analogs (22 took IAsp and 24 took insulin lispro) as bolus insulin; the remaining 121 used human insulin (monophasic and/or biphasic). As a guideline, 40% of daily dose was to be provided at breakfast, 20% at lunch/snack, 30% at dinner, and 10% at bed time (NPH). As treatments were related to meals, subjects were allowed to vary the total daily dose according to their needs. Glycemic goals, which remained the same throughout the study, were to achieve a fasting blood glucose level below 8 mmol/L and a postprandial glucose level below 10 mmol/L. The dose adjustments were based on glycemic goals, HbA1c, and frequency of hypoglycemic episodes.

Measurements

Height and weight were measured at screening, at randomization, and after 6 and 16 wks of treatment. Two eight-point blood glucose profiles were taken at home by the subjects: the first on a normal week day before randomization and the second before the last visit. Measurements were taken before and 90 min after each of the three main meals, at bed time and at 02:00 hours. 'Average postprandial glucose increment' was calculated as the mean difference between the blood glucose values measured 90 min after and before each meal. The subjects were encouraged to measure blood glucose before each meal according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (10) but except for the two visits mentioned any such measurement was not transcribed into the case report form. All hypoglycemic episodes were reported by the family and confirmed by blood glucose testing whenever possible. Episodes were classified as major (subjects unable to treat themselves), minor (blood glucose <2.8 mM, but subjects able to treat themselves) or symptoms only (blood glucose >2.8 mM or not measured) and subjects able to treat themselves. HbA1c was measured at baseline and after 6 and 16 wks by MDS Pharma Services (Central Laboratory) with a validated BIO-RAD Diamat method (reference range 4.8–6.7%).

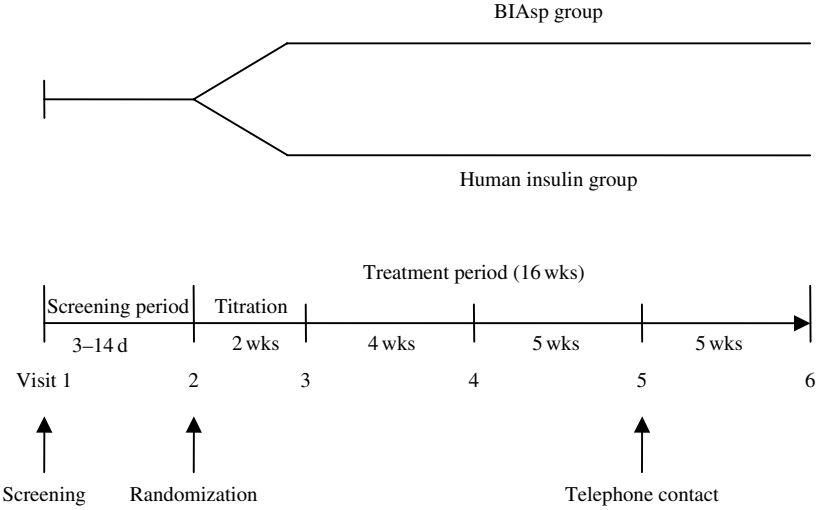

Fig. 1. Study design. BIAsp, biphasic insulin aspart.

Statistical methods

The number of subjects required for the trial was estimated based on the average postprandial glucose increase. Based on previous experience from other clinical trials, a treatment difference between the two groups of at least 1.0 mmol/L could be expected, and allowing for a 10% dropout, a total of 156 subjects was expected to yield a sufficient power to detect this difference. The treatment protocol stated that efficacy and safety analyses should be carried out on all subjects exposed to the treatment drugs. Furthermore, a specific comparison of treatments was performed on the subject population who were treated as specified in the protocol. The average postprandial glucose increment was analyzed by an analysis of covariance model with treatment group and country as fixed effects and with the average postprandial glucose increment at baseline (randomization visit) and HbA1c at last visit as covariates. The adjustment for baseline average postprandial blood glucose increment was used in order to obtain comparable data for analysis in the two groups, and adjustment for the last visit HbA1c was chosen in order to adjust for group differences regarding metabolic control. The purpose of the present study was not to compare the diabetes management in different centers. Therefore, the country was included as a factor in the statistical model, implying that the HbA1c and body mass index (BMI) measurements were evaluated within country but combining information from all countries. The incidence of hypoglycemic episodes was analyzed using a Poisson log linear regression model, with treatment and country as effects. The analysis included subanalyses on daytime (06:01–23:59 hours) and nocturnal (0:00–06:00 hours) episodes. The time to first major hypoglycemic episode was analyzed by a Cox regression model.

The change in BMI in the two treatment groups during treatment adjusted for baseline country, and last visit HbA1c was analyzed and compared. Due to the substantial fluctuations in BMI in children of different ages and sex, this analysis was supplemented, with an analysis based on BMI-standard deviation score (SDS) values. BMI-SDS is a normalized age-adjusted BMI calculated based on BMI values obtained, taken from a reference source. The reference source chosen was the British population described in the paper of Cole et al. (11).

The statistical analyses were performed using SAS version 8.2 on Windows. A significance level of 5% was used throughout the analyses.

Results

The majority of the 167 subjects included completed the trial. However, only 138 received the intended regimen, one main reason being that 17 subjects in the human insulin group were treated for a period with premixed human insulin twice daily instead of once daily, as stated in the protocol. Table 1 summarizes that most of the demographic characteristics at baseline (age, BMI, and HbA1c) were similar in the two treatment arms, but the male/female ratio was slightly different (37/49 in the BIAsp group and 43/38 in the human insulin group).

No statistically significant differences in blood glucose control were found between the two treatment regimens. HbA1c decreased by about 0.2% in both treatment groups from baseline to 16 wks of treatment. At the end of the trial, there was no significant difference between the treatment groups (Table 2). The between-group differences in HbA1c (and in blood glucose) were also non-significant for the subjects following the intended regimen (data not shown).

During the trial, the average postprandial increment in blood glucose was reduced in both treatment groups (Table 3).

Table 1. Demographic characteristics

	BIAsp	Human insulin	Total
Male /female	37/49	43/38	80/87
Age in years*	14.27 (1.95)	14.61 (1.89)	
Body mass index (kg/m^2)	21.16 (3.75)	21.18(2.79)	
Baseline HbA1c(%)	9.70 (1.52)	9.55 (1.59)	

BIAsp, biphasic insulin aspart;HbA1c, hemoglobin A1c; SD, standard deviation.
*Data are mean (SD).

Table 2. Mean HbA1c during treatment

	BIAsp	Human insulin
Baseline		
n	85	81
Mean (SD)	9.70 (1.52)	9.55 (1.59)
6 wks		
n	84	75
Mean (SD)	9.57 (1.50)	9.28 (1.60)
16 wks		
n	83	76
Mean (SD)	9.51 (1.51)	9.37 (1.54)
Adjusted mean* at 16 wks		
Mean(SEM)	9.39 (0.14)	9.30 (0.15)
$p = 0.62$ (ANCOVA adjusted for baseline HbA1c and country)		

ANCOVA, analysis of covariance; BIAsp, biphasic insulin aspart; HbA1c, hemoglobin A1c; SD, standard deviation; SEM, standard error of the mean.
*Least square mean.

Table 3. Average postprandial blood glucose increment

	BIAsp	Human insulin
6 wks		
n	81	72
Mean (SD)	1.34 (3.45)	1.89 (3.26)
16 wks		
n	76	70
Mean (SD)	0.43 (3.28)	0.78 (2.69)
Adjusted mean* at 16 wks		
Mean (SEM)	0.37 (0.41)	0.77 (0.44)
$p = 0.47$ (ANCOVA adjusted for baseline, country, and last visit HbA1c)		

ANCOVA, analysis of covariance; BIAsp, biphasic insulin aspart; HbA1c, hemoglobin A1c; SD, standard deviation; SEM, standard error of the mean.
*Least square mean.

Initially, the two groups received similar doses of insulin, but during the 2-wk titration period, the dose increased more in the BIAsp treatment arm. During the remaining 14 treatment weeks, the dose increased about 8% in both groups, from 1.11 to 1.20 IU/kg in the BIAsp group and from 1.06 to 1.15 IU/kg in the human insulin group.

The analysis of the changes in BMI in the two treatment groups showed that the increase in BMI was smaller in the BIAsp group than in the human insulin group (Table 4). This difference was significant ($p = 0.007$) for males but not for females. The result of the overall conclusion was confirmed by an overall analysis based on BMI-SDS showing a statistically significant difference ($p = 0.01$) between the two treatment groups (data not shown).

The number of adverse events was comparable between treatment groups, and the majority of events

Table 4. Change in body mass index (BMI) during treatment

	BIAsp	Human insulin	
Baseline			
n	86	81	
Mean (SD)	21.16 (3.75)	21.18 (2.79)	
16 wks			
N	84	76	
Mean (SD)	21.30 (3.65)	21.56 (2.89)	
Adjusted* increase and analysis at 16 wks			
All	85	77	
Increase (SEM)	0.16 (0.10)	0.56 (0.11)	$p = 0.005$
Males	36	40	
Increase (SEM)	−0.13 (0.16)	0.41 (0.18)	$p = 0.007$
Females	49	37	
Increase (SEM)	0.21 (0.14)	0.43 (0.16)	$p = 0.276$

BIAsp, biphasic insulin aspart; HbA1c, hemoglobin A1c; SD, standard deviation; SEM, standard error of the mean.
The analysis was adjusted for baseline, country, and HbA1c at last visit.
*Analysis of covariance for all subjects and for males and females separately.

were mild or moderate. Only a few events, two in the BIAsp and six in the human insulin group, were considered to be treatment related.

The rate of hypoglycemic episodes was similar in the two treatment groups, both during the day and during the night. However, the nightly rate of episodes was 10 times lower in both groups (Table 5). An analysis of the time to first major hypoglycemic episode based on a total of 15 episodes showed that the relative risk of experiencing a major episode was not significantly different in the two treatment groups. Although the number and severity of hypoglycemic episodes were similar in the two treatment groups, the distribution of episodes between the subjects was skewed. Ten subjects (six in the BIAsp group and four in the human insulin group) accounted for more than 600 episodes, 382 and 221 episodes, respectively, or almost 30% of all episodes. The majority of these episodes were classified as symptoms only.

No clinically relevant abnormalities were registered in any of the treatment groups at the physical examinations.

Discussion

Type 1 diabetes is typically diagnosed early in life, and it is therefore important to offer treatment regimens that are easy to handle, particularly for children and adolescents. Adolescence is a period with sudden physical and physiological changes which are often associated with increased insulin resistance, especially in girls (3, 5). It is also a period with a change in lifestyle from childhood, with its parentally controlled daily rhythm of regular meals and preplanned activities, to a less-structured lifestyle with irregular meals and more spontaneous activities, including exercise. It is important, therefore, to evaluate the efficacy and

Table 5. Frequency of hypoglycemic episodes

	BIAsp			Human insulin		
Exposed subjects	n = 86	(%)	E	n = 87	(%)	E
Episode numbers						
Major episodes	6	(7)	7	3	(4)	8
Minor episodes	70	(81)	432	57	(70)	428
Symptoms only	66	(77)	726	59	(73)	567
Episode rates		R			R	
All episodes		4.17	1165		4.30	1002
Daytime episodes		3.93	1098		3.98	929
Nocturnal episodes		0.24	67		0.31	73

BIAsp, Biphasic insulin aspart.
n – number of exposed subjects with episode.
(%) – proportion of exposed subjects with episode.
E – number of hypoglycemic episodes.
r – rate of hypoglycemic episodes (episodes per month of exposure).

safety of new insulin analogs and treatment regimens for this age group.

The overall impression obtained from this comparison between meal-related treatment with BIAsp 30 or human insulin is that the two treatments are very similar with respect to efficacy and safety. The mean values for blood glucose and HbA1c values were high in both treatment groups, both initially and during the trial, illustrating that compared with adults, optimization of blood glucose control is particularly difficult in adolescents (3). In another trial with adolescents, Dorchy et al. (12) obtained more impressive results with respect to HbA1c with a basal-bolus treatment regimen, and it was shown that HbA1c reduction was correlated to intensity of home blood glucose measurements. Data from the two trials should, however, be compared very cautiously. The baseline value of HbA1c was much lower in the Dorchy trial, indicating an initially better controlled and possibly more compliant trial population; moreover, the focus of that trial was the effect on HbA1c rather than on prandial blood glucose. Recent data from a trial in an adult population with type 1 diabetes showed an improved effect on HbA1c using IAsp together with insulin detemir in a basal-bolus treatment scheme compared with regular human insulin + NPH (13). The associated problems already mentioned with the treatment of adolescents (14) and the fact that the adult population in the Hermansen trial (13) were in better control at baseline than the adolescents in the current trial, again, make it very difficult to compare the trial results.

Both treatments in the current trial were associated with overall improvements of prandial blood glucose control and small reductions in HbA1c. This might be a result of close monitoring (several daily home measurements with glucose monitor) and frequent dose adjustments (intensively in the titration period – first 2 wks of treatment – and subsequently according to individual needs) in both groups. The incidence of adverse events was low in both groups. One problem with the interpretation of the hypoglycemia data is associated with the age of the subjects. Adolescents are normally capable of handling injections by themselves but not always experienced enough to handle hypoglycemic episodes without assistance. Additionally, when it comes to their perception of hypoglycemia, they may be highly influenced by their parents. It is striking that the distribution of hypoglycemic episodes in this trial was skewed: most subjects experienced only a few episodes, but a few subjects had a high number of episodes. Most of these episodes were classified as symptoms only (i.e., not supported by glucose measurements) and in an adult population might not have been reported at all. On the other hand, major episodes, which were defined as episodes where the subjects are not able to treat themselves, might have been over-reported in the adolescents in cases where they were assisted, even though they might have been able to handle the episode alone. Major hypoglycemic episodes did not appear to be related to the type of treatment.

In both treatment groups, the 16-wk treatment period was associated with a minor increase in BMI; however, the increase in the human insulin group was significantly higher than in the BIAsp group. Intensive insulin regimens are often associated with a slight increase in BMI, and snacking between meals has been used as an explanation for this increase (3, 11, 15, 16).

The human insulin treatment scheme requires injections 30 min before each major meal (i.e., it requires forward planning). When planning fails for some reason, the teenager's attitude toward snacking may be become more relaxed and might easily result in an increase in weight and BMI. For an adolescent, the BIAsp treatment scheme with injections taken immediately before the major meals might be easier to fit in with a normal daily life where there are no preplanned meal times, and this, in turn, might reduce the need for snacking. In general, BMI increased less in males than in females. This difference between genders might be associated with a relative lack of physical activity in teenage girls and abnormal eating behaviors (17, 18). Furthermore, it has recently been shown that teenage girls had a poorer health perception and more difficulties with diabetes control than males (14).

In conclusion, adolescents on multiple daily injections of BIAsp insulin achieved a similar blood glucose control and experienced a similar rate of hypoglycemic episodes as the group treated with human insulin. However, due to the fast action, the rapid-acting analog is more convenient to use before meals. A lesser increase in BMI in the BIAsp group may be related to more convenient timing (immediately before as opposed to 30 min before meals) of insulin administration in this group.

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