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An exploratory study of the effect of using high-mix biphasic insulin aspart in people with type 2 diabetes

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Objective: To compare blood glucose control when using biphasic insulin aspart (BIAsp) three times a day (using 70/30 high-mix before breakfast and lunch), with biphasic human insulin (BHI, 30/70) twice daily in adults with type 2 diabetes already treated with insulin.

Research design and methods: In a 60-day, open-label, crossover study, people with insulin-treated type 2 diabetes [n = 38, baseline haemoglobin A1c 8.3 ± 0.9 (s.d.) %] were randomized to BIAsp three times a day before meals, as BIAsp 70 (70% insulin aspart and 30% protamine-complexed insulin aspart) before breakfast and lunch and BIAsp 30 (30/70 free and protamine-complexed insulin aspart) before dinner, or to human premix insulin (BHI) 30/70 twice a day before meals. A 24-h in-patient plasma glucose profile was performed at the end of each 30-day treatment period. The total daily insulin dose of BIAsp regimen was 110% of BHI and the doses were not changed during the study.

Results: There was no difference between BIAsp and BHI in geometric weighted average serum glucose over 24 h [7.3 vs. 7.7 mmol/l, BIAsp/BHI ratio 0.95 (95% CI 0.88–1.02), not significant (NS)], but daytime geometric weighted average glucose concentration was significantly lower with the BIAsp regimen than with BHI [8.3 vs. 9.2 mmol/l, BIAsp/BHI ratio 0.90 (0.84–0.98), p = 0.014]. The mealtime serum glucose excursion was also lower with BIAsp than with BHI with statistically significant differences at lunchtime [difference −4.9 (−7.0 to −2.7) mmol/l, p = 0.000); the difference in glucose excursions above 7.0 mmol/l was also significant [−5.8 (−8.3 to −3.2) mmol/l, p = 0.000). The proportion of participants experiencing confirmed hypoglycaemic episodes was similar between regimens (42 vs. 43%, NS).

Conclusions: An insulin regimen using high-mix BIAsp (BIAsp 70) before breakfast and lunch and BIAsp 30 before dinner can achieve lower blood glucose levels during the day through reduced mealtime glucose excursions in particular at lunchtime than a twice-daily premix regimen.

Keywords: biphasic insulin aspart, high-mix, premix insulin, type 2 diabetes

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Introduction

Clinical studies have supported the view that better control of blood glucose levels in people with type 2 diabetes reduces the incidence and progression of late-developing microvascular complications [1,2]. Type 2 diabetes is a progressive condition and oral glucose-lowering drugs fail to control hyperglycaemia with time [3] such that insulin therapy is needed. Conventionally, some of these people have been treated with twice-daily injections of premixed (biphasic) human insulin ('human premix'), particularly where endogenous insulin secretion is unable to provide adequate prandial insulin delivery. However, in many people twice-daily human premix

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cannot normalize mealtime glucose excursions without significant risk of hypoglycaemia. Substituting a biphasic insulin analogue mixture (insulin aspart or insulin lispro; 'biphasic analogue') has consistently resulted in statistically significant improvements in postmeal blood glucose control [4,5]. However, although starting glucose levels with analogue premix are lower before lunch, the glucose excursion will if anything be higher, as there will be no mealtime insulin absorption continuing from breakfast. Accordingly, peak postlunch glucose levels are similar to those found with the human premix [4,5]. Analogue regimens can, however, still be advantageous over human premixes in reducing hypoglycaemia, particularly major and nocturnal hypoglycaemia in line with findings for rapid-acting analogues in other situations [6–8].

Where it is clinically important to deal with the problem of meal-related glucose excursions more than one approach is possible. One such is to move to a four injection mealtime + basal regimen, but if this is not acceptable then simple addition of a lunchtime rapid-acting insulin analogue might be appropriate. If this latter approach is used then the opportunity can also be taken to reduce the effect of the peak of action of the protamine-bound part of the biphasic mixture, distributing it between both the breakfast and the lunchtime injections [9–11], while using an insulin mixture with proportionately less of the intermediate-acting component. Giving the protamine-bound component as two injections will also theoretically reduce the variability of absorption of this component by around 1.4 ($\sqrt{2}$) times. This approach is investigated in the current study.

To balance insulin delivery between meal and basal requirements, and as some interprandial insulin would be then contributed by the rapid-acting analogue component, a 70 : 30 (rapid acting: protamine complexed, high mix) preparation was chosen for this exploratory study. This, however, was reversed with the evening meal to enable provision of sufficient basal insulin overnight.

Research Design and Methods

The study used a 60-day, open-label, randomized, two-way crossover design in people with type 2 diabetes studied at a single centre at Newcastle University. Having two vs. three insulin injections precluded blinding as insulin doses had to be adjusted to suit the different regimens. Treatment order was allocated by formal randomization from a remote location. The local ethics committees approved the study before any trial activity, which began only after written informed consent was obtained from each participant.

Study Participants

Thirty-eight people were recruited after preliminary screening. Seven of these did not fulfil study inclusion criteria; thus, 31 people were randomized between study arms. During the first treatment period, two participants were withdrawn for protocol violations and one withdrew for personal reasons; all three were using biphasic insulin aspart (BIAsp) treatment at the time of withdrawal. During the second treatment period, two participants on biphasic aspart and one on human premix had endpoint blood samples lost because of freezer failure and one further participant suffered severe protocol violation. Thus, paired endpoint data were available on 24 people.

The people recruited were men and women aged 18–75 year with type 2 diabetes (meeting the World Health Organization definition of diabetes [12]) who had been using a human premix for at least 3 months and who had an haemoglobin A1c (HbA_{1c}) $\leq$ 10.0% and a body mass index $\leq$ 35.0 kg/m^2 (table 1). Women of childbearing potential were required to be using adequate contraception. Significant hepatic or renal dysfunction, or active cardiovascular disease, was exclusion criteria.

Insulin Preparations

In this study, premix human insulin injection was compared with premix aspart insulin. The premix human insulin used was a suspension/solution of 30% human insulin and 70% protamine-complexed human insulin (Mixtard 30; Novo Nordisk, Bagsvaerd, Denmark). The premixed insulin aspart used was of two types: premixed aspart 70 (BIAsp 70) was a mixture of 70% aspart insulin and 30% protamine-complexed aspart insulin (Novo Nordisk); premix aspart 30 (BIAsp 30) was a mixture of 30% aspart insulin and 70% protamine-complexed aspart insulin (NovoMix 30; Novo Nordisk). All insulin preparations were given using the same types of pen injector (NovoPen 3; Novo Nordisk) and needle.

Table 1 Characteristics of the people with type 2 diabetes randomized and treated (the intention-to-treat population)

Participants (n)	31
Sex (male : female)	20 : 11
Age (year)	63.8 ± 9.8
Weight (kg)	82.9 ± 10.9
BMI (kg/m^2)	30.0 ± 3.5
HbA_{1c} (%)	8.3 ± 0.9
Duration of diabetes (year)	12.0 ± 5.5

Data are mean ± s.d. or number. Haemoglobin A1c (HbA_{1c}) normal range <6.1%.

Sulfonylureas were discontinued before the study. Seventeen participants remained on metformin throughout the study and one on acarbose.

Study Design

After an 8-day run-in period, during which previous insulin therapy was continued, participants were randomized to BIAsp thrice daily or human premix twice daily, BIAsp was administered as BIAsp 70 before breakfast and lunch and BIAsp 30 before dinner, while human premix was given before breakfast and dinner as a conventional comparator. Insulin was to be injected within 5 min before the meal and the site of injection (either abdomen or thigh) was kept the same through the trial. At the randomization visit, the doses of human premix were set to those being used previously, but the dose of BIAsp was increased by 10% of the previous total daily dose and was then split into BIAsp 70, 70 and 30 in the ratio of 35 : 25 : 50. At the crossover visit (visit 4) after 30 days, the dose of insulin was reduced back to 100% for people changing from BIAsp to human premix but increased by 10% and split into three doses for the other group as above.

Participants were asked to perform daily self-monitoring of capillary blood glucose levels before meals using the One-Touch blood glucose meter (Lifescan, High Wycombe, UK).

Study visits occurred every 15 days during 2- × 15-day treatment periods, with telephone consultation between visits. At each consultation, self-monitored blood glucose levels and insulin doses were reviewed, and the insulin dose was kept constant unless otherwise indicated for safety reasons.

24-Hour In-patient Plasma Glucose Assessment

At the end of each 30-day treatment period, participants were admitted for 24-h in-patient plasma glucose assessment. They attended 1 h before the usual time of their evening meal. Blood was taken using a intravenous cannula (Vasofix; Braun, Melsungen, Germany) for measurement of plasma glucose, insulin and C-peptide concentration every 15 min for 2 h after breakfast and dinner, every 30 min for 2 h after lunch and hourly otherwise. A choice of meals was provided at 18:00, 08:00 and 13:00 hours, but identical meals were provided for the second 24-h profile. At the end of the first 24-h study, patients commenced the alternative insulin regimen and the study sequence was repeated.

Measurements

Hypoglycaemia was classified as symptoms only (with glucose levels >2.8 mmol/l or not measured), minor confirmed (≤2.8 mmol/l) or major (requiring third party assistance).

For the 24-h studies, plasma glucose concentrations were measured by a glucose oxidase method at a central laboratory (Nova Medical Medi-Lab, Copenhagen, Denmark) blind to insulin treatment. Serum insulin was measured using a Pharmacia RIA kit (Pharmacia, Uppsala, Sweden) without correction for differences in cross-reactivity for insulin aspart compared with human insulin and C-peptide by ELISA (K6218; Dako, Ely, UK).

Statistical Analysis

The primary efficacy assessment was weighted mean daily plasma glucose measured from the 24-h profile at the end of each treatment period. This and other measures were analysed using an analysis of variance (ANOVA) model with a fixed period effect, a random participant effect and constant measurement error. Using a s.d. of average 24-h serum glucose from previous studies of 1.5 mmol/l, and a significance level of 5%, a sample size of 24 patients was selected to detect a true treatment difference in average plasma glucose of 1.31 mmol/l between insulin regimens, with a statistical power of 80%. Wherever appropriate, logarithmic transformation of data was performed or non-parametric methods used. The data were analysed on intention-to-treat basis (all participants randomized).

Secondary efficacy assessments included premeal glucose concentrations before breakfast, lunch and dinner, glucose excursions over the 4 h after main meals and the glucose excursions >7.0 and <3.0 mmol/l for these periods. Secondary pharmacokinetic endpoints included maximum concentrations of serum insulin after meals, and the time of this, together with the area under the 24-h insulin concentration time curve.

Carry-over effects were not expected as insulin dose changes were determined by protocol at randomization and treatment change over (see above) and not adjusted otherwise. Likewise, period effects were not expected; a check for this was made in the ANOVA model. Data are stated as mean ± s.e. and mean difference (95% CI) unless otherwise stated.

Results

Insulin Doses

Mean daily dose on the biphasic aspart regimen at the end of the treatment periods was 0.97 U/kg and on human premix 0.88 U/kg, as determined by the protocol.

24-Hour Serum Glucose Profile

Geometric mean 24-h plasma glucose concentration did not differ between regimens [BIAsp vs. biphasic human insulin (BHI) 7.3 vs. 7.7 mmol/l, ratio 0.95 (95% CI 0.88–1.02), not significant (NS)] (table 2). However, mean daytime (08:00–22:00 hours) plasma glucose concentration was statistically significantly lower for BIAsp than with the BHI [8.3 vs. 9.2 mmol/l, ratio 0.90 (0.84–0.98), p = 0.014]. During the night (22:00–08:00 hours), levels were very similar [5.8 vs. 5.6 mmol/l, ratio 1.05 (0.94–1.16), NS].

The mean serum glucose profiles for the two treatment regimens are shown in figure 1. Visual inspection reveals that the mean glucose values after dinner appear to be higher after treatment with BHI 30 than with BIAsp 30 until approximately 01:00 hours, at which point the profiles cross so that somewhat lower glucose concentrations may be seen for the BHI treatment for the rest of the night. At breakfast, despite the mean morning prebreakfast serum glucose being 7.3 mmol/l for BIAsp and 6.5 mmol/l for BHI, the peaks of postbreakfast profiles are similar. After lunch, higher glucose values are seen with the BHI treatment (no injection at lunchtime) than with the BIAsp treatment (BIAsp 70 given).

Prebreakfast plasma glucose concentration was higher with BIAsp than with BHI [geometric mean 7.3 vs. 6.5 mmol/l, ratio 1.12 (1.02–1.23), p = 0.021] (table 2). Plasma glucose excursions were not different after breakfast and dinner but were statistically significantly lower for the BIAsp regimen than for human premix at lunchtime, both for the glucose excursion itself and for the excursion above 7.0 mmol/l (table 3).

Serum Insulin and C-peptide

Summary endpoints for serum insulin levels are given in table 4. Statistically significantly higher maximum concentration (*C*max) was seen with BIAsp than with BHI after both breakfast (p = 0.004) and dinner (p = 0.014). After breakfast, the time to maximum concentration (t_{max}) was possibly earlier with BIAsp 70 than with BHI 30 (p = 0.058).

The serum insulin profiles for the two treatments are shown graphically (figure 1). The level is higher for the BIAsp treatment than for the BHI treatment for most of the daytime period, particularly after lunch and dinner, but tends to be lower during the night.

The serum C-peptide profiles are presented in figure 1. Inspection of the mean profile reveals that similar peaks in serum C-peptide are seen after dinner and breakfast for the BIAsp and BHI treatment regimens. However, after lunch, the C-peptide excursion is higher for the BHI treatment regimen than for the BIAsp treatment regimen.

Table 2 Summary of the 24-h in-patient profile plasma glucose endpoints (mmol/l) using the biphasic insulin aspart and human premix regimens

	Biphasic aspart	Human premix	Ratio (95% CI)	p
24 h	7.3	7.7	0.95 (0.88–1.02)	NS
08:00–22:00 hours	8.3	9.2	0.90 (0.84–0.98)	0.014
22:00–08:00 hours	5.8	5.6	1.05 (0.94–1.16)	NS
Prebreakfast	7.3	6.5	1.12 (1.02–1.23)	0.021
Prelunch	5.3	5.6	0.96 (0.81–1.13)	NS
Predinner	5.1	5.6	0.90 (0.77–1.04)	NS

Data are geometric mean ± s.e. or ratio (95% CI).
NS, not significant.

Hypoglycaemia

There were two episodes of major hypoglycaemia on BIAsp. For minor or symptoms only hypoglycaemic episodes, the incidence was numerically higher for the BIAsp treatment than for BHI (12.2 and 14.5 vs. 7.8 and 2.0 events/patient-year), but the number of events was too low to be analysed for statistical significance (table 5). The proportion of participants experiencing minor (confirmed) hypoglycaemic episodes was similar for the two insulin treatments (42 and 43%, NS). However, the proportion of participants reporting episodes as symptoms only (unconfirmed) was higher for the BIAsp treatment than for the BHI treatment (42 vs. 14%, p = 0.001).

In general, there were no major differences between the treatments in the distribution of hypoglycaemic episodes by time of day. In both groups, the proportion of subjects experiencing any type of hypoglycaemia (major, minor and symptoms only combined) was highest in the period 12:00–18:00 hours.

Adverse Events

The proportion of subjects experiencing adverse events was higher for the BHI treatment than for the BIAsp treatment, but this difference could not be attributed to any particular type of event or events related to any specific system organ class.

Discussion

In the present study, we have compared two types of insulin regimen using three different insulin preparations. This is a pragmatic approach to try to establish

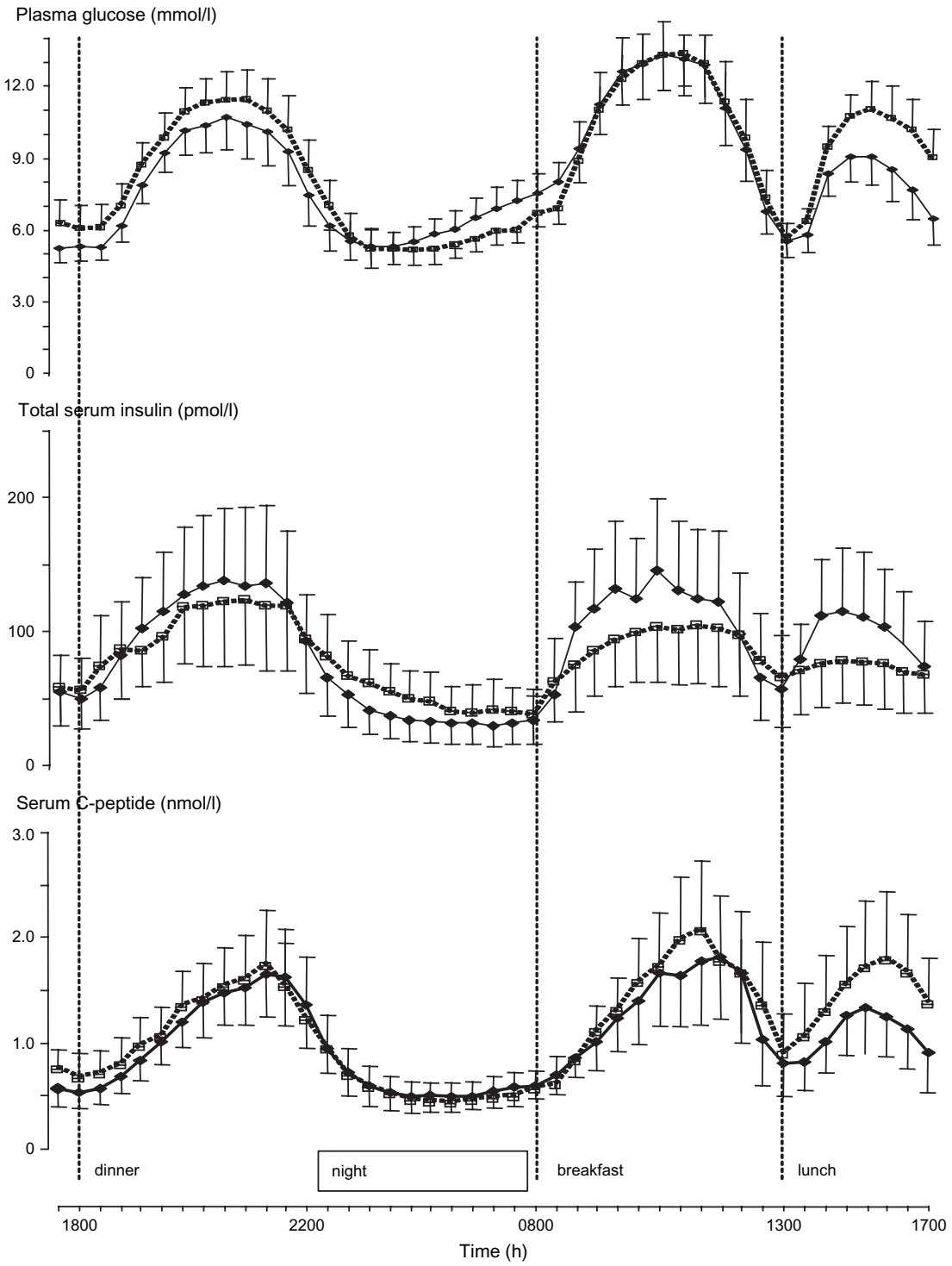

Fig. 1 Twenty-four-hour glucose, insulin and C-peptide concentration profiles in people with type 2 diabetes managed with human premix insulin twice daily ((□·····□)) or high-mix (70/30) biphasic insulin aspart (BIAsp) before breakfast and lunch plus 30/70 BIAsp before the evening meal ((◆——◆)).

Table 3 Mealtime plasma glucose excursion 0–4 h (mmol/l*h) on biphasic insulin aspart and human premix regimens

	Biphasic aspart	Human premix	Ratio (95% CI)	p
After breakfast, mmol/l				
Median	13.6	15.8	−2.4 (−6.2 to 1.0)	NS
>7.0	15.0	12.9	−0.2 (−4.0 to 3.8)	NS
<3.0	0.0	0.0	0.0 (0.0 to 0.0)	NS
After lunch, mmol/l				
Median	9.3	13.6	−5.1 (−7.1 to −3.0)	0.000
>7.0	3.8	11.2	−5.6 (−8.1 to −2.9)	0.000
<3.0	0.0	0.0	0.0 (0.0 to 0.0)	NS
After dinner, mmol/l				
Median	12.9	13.0	−1.4 (−5.3 to2.0)	NS
>7.0	8.1	10.8	−3.2 (−7.5 to 0.8)	NS
<3.0	0.0	0.0	0.0 (0.0 to 0.0)	NS

Data are median or difference (95% CI).
NS, not significant.

a possible role for a novel insulin preparation when compared with a conventional insulin regimen. Thus, among other reasons, the study can only give indicative information as other, untested, insulin regimens might give similar or even better blood glucose control to the novel regimen tested. It is clear from studies of basal insulin alone when initiated in type 2 diabetes that mealtime glucose control often deteriorates during the day [13], suggesting that mealtime insulin is also needed, while studies of premix analogues have suggested that a third, mid-day, injection can be beneficial in some people [9,11]. Logically, the very best application of a high ratio premix might be three times a day before the main meals, combined with basal intermediate-acting insulin a bedtime, but this implies moving to four injections a day and competes head on with a full analogue mealtime plus basal regimen as is now standard in people

Table 4 Serum insulin pharmacokinetic endpoints with the biphasic insulin aspart and human premix insulin regimens

	Biphasic aspart	Human premix	Ratio/difference (95% CI)	p
Breakfast				
T_{max} (min)	90	105	−15 (−30 to 0)	0.058
C_{max} (mU/l)	110	89	1.2 (1.1 to 1.4)	0.004
Dinner				
T_{max} (min)	90	120	−15 (−38 to 8)	NS
C_{max} (mU/l)	116	97	1.2 (1.0 to 1.4)	0.014
24 –h				
AUC_{ins} (mU/l*h)	1213	1182	1.0 (0.9 to 1.1)	NS

Data are median or geometric median or difference/ratio (95% CI).
C_{max}, maximum concentration; NS, not significant, T_{max}, time to maximum concentration. AUC, area under the curve.

Table 5 Hypoglycaemic episodes by treatment periods on the biphasic insulin aspart and human premix regimens

	Biphasic aspart (n = 31)			Human premix (n = 28)		
	People, n (%)	Events (n)	Incidence (pt/year)	People, n (%)	Events (n)	Incidence (pt/year)
Hypoglycaemia						
Major	1 (3)	2	0.8	0 (0)	0	0.0
Minor	13 (42)	32	12.2	12 (43)	20	7.8
Symptoms only	13 (42)	38	14.5	04 (14)	5	2.0

with Type 1 diabetes. An earlier study had attempted to use a 50 : 50 mixture of BIAsp at the time of the evening meal, but, by comparison with human premix, pre-breakfast plasma glucose control was much poorer, reflecting the deficiency in intermediate-acting insulin in the evening [10]. Accordingly, the present study design, was an attempt to examine possible benefit for people with type 2 diabetes from a high-mix ratio while only requiring one extra daytime injection, and its further examination would require comparison to other alternative regimens such as analogue 30/70 mixtures two or three times daily.

A further compromise of design was the use of semi-fixed insulin doses. This has the advantage in a short study with in-patient 24-h profiling of avoiding the loss of study power that can occur with trials of insulin dose adjustment, but also means that, where the insulin regimens are different in the two arms, the doses used have to be preset rather than optimized. As a result, while insulin dose for the standard comparator has been optimized in clinical practice over some months or years, the novel regimen is not so optimized and hence disadvantaged. Set against this in the current study was an overall insulin dose increase of some 10%, chosen on the basis that an increase in injection number reduces the effect of variability of insulin absorption, and that analogue regimens anyway appear to give less hypoglycaemia [6,8,14–16].

One of the limitations of this study is the need to use the high-mix preparation in context, resulting in an increase in the number of injections from two to three, allowing an increase in daily dose of 10% and a change from human to premix analogue insulin. This makes it difficult to assess with certainty the effect of individual interventions in other contexts but does establish the properties of the new preparation when used in this way.

The primary endpoint of the average 24-h plasma glucose did not differ statistically between the two regimens (table 2), but the numerical reduction on the BIAsp regimen is consistent with the finding of an average daytime (08:00–22:00 hours) glucose concentration 0.9

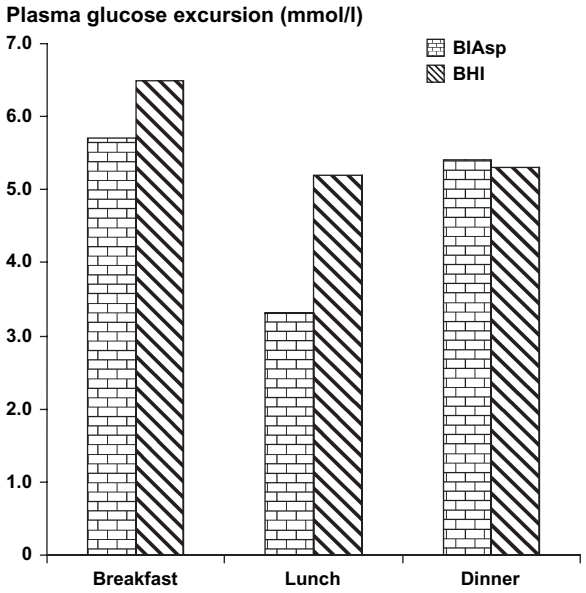

Fig. 2 Peak rise in plasma glucose with each of the three main meals in people with type 2 diabetes managed with human premix insulin twice-daily or high-mix (70/30) biphasic insulin aspart (BIAsp) before breakfast and lunch plus 30/70 BIAsp before the evening meal. BHI, biphasic human insulin.

mmol/l lower with BIAsp than human premix. Such a difference might be clinically relevant, particularly as it appears because of a reduction of exposure to the highest (and thus most toxic) glucose levels of the day, the peaks after meals (figures 1 and 2) [17].

Inspection of the glucose profiles towards the end of the night suggests much more marked deficiency in insulin action at this time in the BIAsp group. This, given the half-life of action of insulin (approximately 20 min), will have a marked influence on the size of the breakfast glucose excursions. Although the breakfast BIAsp 70 dose was lower than the BHI 30 dose, the higher content of the mealtime component and fast action of the rapid-acting analogue are reflected in the serum insulin profiles (figure 1) and this counters the greater premeal insulin deficiency to give nearly equivalent plasma glucose excursions after breakfast.

As noted above, while high-mix insulin preparations further enhance the control of mealtime plasma glucose excursions, the problem can be end-of-night hyperglycaemia if a low ratio of the intermediate component is given in the evening. Thus, in an earlier study, when BIAsp 50 was given at dinner, the mean fasting glucose level was 10.7 mmol/l and 10.2 mmol/l when BIAsp 70 was given [10]. In the present study, end-of-night (prebreakfast) plasma glucose levels were much more satisfactory, although the geometric mean level still statistically significantly higher (7.3 mmol/l; table 2) on the high-mix regimen.

The results in the current study are broadly in line with a study conducted in parallel, although in a mixed population of people with type 1 and type 2 diabetes [9]. In that trial which compared a choice of one of two higher mix BIAsp regimens to human premix, the majority of participants on the analogue regimen were transferred to the low ratio (30/70) biphasic aspart before the evening meal treatment to attempt to maintain prebreakfast plasma glucose levels to target. Used this way overall blood glucose control (HbA_{1c} and mean of an 8-point blood glucose profiles) was better with the BIAsp treatment, even though prebreakfast self-monitored levels were higher.

In the current study, the number of major hypoglycaemic events was too small to be meaningful. Indeed, the study lacks any power to provide reliable estimates of the prevalence and incidence of hypoglycaemia between regimens. Nevertheless, while the proportion of participants who experience confirmed (minor) hypoglycaemia was similar between regimens, the numerical trend is for them to have more episodes when using the BIAsp regimen. This is particularly true for unconfirmed, symptoms only hypoglycaemia and it is difficult to know whether, in this open-label short-term study, the use of a novel insulin, three injections a day and a higher total dose might have led to a higher rate of attribution of day-to-day symptoms to hypoglycaemia. Similarly, indeterminate results were reported by Clements *et al.* [9]. This matter is of concern and could only be tackled by further, longer term studies with careful confirmatory testing of all suspicious symptoms.

The analyses of the pharmacokinetic endpoints were performed using serum insulin levels measured on a human insulin assay without any adjustment for aspart cross-reactivity, an adjustment that would be expected to raise BIAsp values higher. Nevertheless, the mean maximum concentration at both breakfast and dinner was already measured as higher for BIAsp compared with human premix, as expected. Indeed, the serum insulin profile in general were both in line with expectations based on known pharmacokinetic properties of rapid-acting insulin analogues when compared with human insulin and in agreement with the 24-h plasma glucose profiles [18]. On visual inspection, serum C-peptide levels were similar on the two profiles (figure 1), except after lunch where the higher plasma glucose levels on the human premix regimen appears to lead to some compensatory endogenous insulin secretion.

In conclusion, this study suggests that a thrice-daily analogue-based BIAsp regimen using high ratio free: protamine-complexed insulin with about 10% daytime insulin dose increase can trim postlunch glucose excursions when compared with a conventional human premix regimen. However, the utility of and safety of the regimen would need longer study to define which groups of people with type 2 diabetes might benefit, particularly by comparison with a thrice-daily conventional (30/70) biphasic analogue regimen. Meanwhile, the study suggests the possibility of added utility from the use of high ratio mixtures, something that is likely to be particularly appropriate to future long-acting insulin analogues, designed to be both of true 24-h duration and capable of premixing with rapid-acting insulin.

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