A Comparison of Postprandial and Preprandial Administration of Insulin Aspart in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE — The aim of this study was to compare the glycemic control of preprandial versus postprandial injections of the new rapid-acting insulin analogue aspart in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Forty-two children (aged 6–12 years) and 34 adolescents (13–17 years) were randomized to preprandial (immediately before meal start) and postprandial (immediately after a meal or a maximum of 30 min after meal start) treatment with insulin aspart (at least thrice daily) as part of a basal/bolus regimen in a multicenter study with an open labeled, two-period cross-over design (6-week periods). Of this group, 49% were boys, 55% were aged ≤13 years, and duration of diabetes was 4.4 years (range 1.0–9.4).

RESULTS — Glycemic control for postprandial treatment was not worse than preprandial treatment as assessed by fructosamine week 0 vs. 6 (mean ± SD, preprandial 367 ± 74 vs. 378 ± 90 μmol/l; postprandial 383 ± 83 vs. 385 ± 77 μmol/l) and HbA_{1c} (preprandial 7.9 ± 1.3 vs. 8.0 ± 1.5%; postprandial 8.0 ± 1.4 vs. 8.3 ± 1.5%, $P = 0.14$). The only statistically significant finding from the seven-point blood glucose profiles and derived parameters between preprandial and postprandial treatment was a lower postprandial glucose level 120 min after breakfast (mean ± SEM, −2.08 ± 0.74 mmol/l, $P = 0.016$). The relative risk of hypoglycemia (blood glucose <3.9 mmol/l) preprandially to postprandially was not significantly different (mean 1.1; 95% CI 0.91–1.35; $P = 0.31$). Overall treatment satisfaction was equally high for both regimens with both patients and parents.

CONCLUSIONS — Although preprandial administration of insulin aspart is generally preferable, this study shows that in children and adolescents, postprandial administration of insulin aspart is a safe and effective alternative.

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Abbreviations: AE, adverse event; DTSQ, Diabetes Treatment Satisfaction Questionnaire; IAsp post, postprandial administration of insulin aspart; IAsp pre, preprandial administration of insulin aspart; PP, per protocol.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Insulin aspart is a rapid-acting human insulin analogue designed to display improved subcutaneous absorption properties compared with human insulin. In insulin aspart, the amino acid in the B28 position, proline, has been replaced by aspartic acid, resulting in a reduced tendency of the insulin molecule to self-associate (1). Insulin aspart provides a remarkably shorter time to maximum effect and has a shorter duration of action compared with human insulin. This results in improved postprandial glycemic control as compared with human insulin administered within 30 min before a meal, even when insulin aspart is administered immediately before a meal (2). Recently, the introduction of another rapid-acting insulin analogue, insulin lispro, was associated with a significant improvement in glycemic control (an observational study from a large pediatric diabetes center [3]). Although minimal differences in the pharmacological profile of both types of rapid-acting insulin analogues have been described (4–6), to date no studies on clinically relevant differences have been published.

Pharmacokinetic data of rapid-acting insulin analogues in children and adolescents are only available for insulin aspart. This has been investigated in 18 children and adolescents age 6–17 years. Insulin aspart was rapidly absorbed and eliminated. Corresponding to pharmacokinetics in adults, the maximum plasma concentration of insulin aspart was approximately twice that of human insulin, and maximum concentration was reached at a median of 40 min with insulin aspart compared with 75 min with human insulin (7). Interestingly, an age dependency was found with higher maximal insulin concentrations and higher bioavailability in adolescents of both aspart and regular insulin. This demonstrates that pharmacokinetic and pharmacodynamic results from adults cannot readily be transferred to children. Although the optimal time of

administration of insulin aspart is immediately before meals, premeal dosing implies meal size adjustment to dose, which is not always possible, especially in children. The rapid absorption of insulin aspart may offer advantages of meal size-adjusted dosing, and a relatively small difference in postprandial glycemic control may be outweighed by such dose adjustment according to the actual food intake rather than an incorrect dose based on expected meal intake.

Therefore, this trial aimed to compare the glycemic control and safety profile of insulin aspart when administered postprandially and preprandially in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Design

This was a randomized, open-labeled, cross-over trial comparing the efficacy and safety of insulin aspart (NovoRapid/NovoLog; Novo Nordisk, Bagsvaerd, Denmark) administered before meals (IAsp pre) or after meals (IAsp post) in type 1 diabetic children and adolescents (age 6–17 years). The trial comprised one screening visit (visit 1), two treatment periods (visits 2–3 and 3–4), and a follow-up visit (visit 5). The trial was conducted at nine trial sites: two in Austria (15 and 10 subjects), four in Germany (7, 5, 7, and 8 subjects), and three in Sweden (8, 8, and 8, subjects). Insulin aspart was provided in 100 U/ml 3.0-ml Penfills for use with a Novo Nordisk injection device (NovoPen 3). The protocol, consent form, and subject information sheet were approved by the respective health authorities and local ethics committees according to local regulations. Assent and written informed consent were obtained from all subjects and/or from a legal representative before initiation of any trial-related activities, and the trial was performed in accordance with the principles of Good Clinical Practice (8), the Declaration of Helsinki (9), and its amendments in force at the initiation of the trial (10 February 2001).

Subjects

Subjects were included according to the following criteria: children (age 6–12 years) and adolescents (age 13–17 years) diagnosed with type 1 diabetes for at least 12 months, being on intensive basal/bolus insulin treatment regimen (at least three daily meal-related injections of short-acting insulin) for at least 1 month and with HbA_{1c} ≤12.5% at the time of inclusion. Subjects were not included in the trial if they: had a total daily insulin dose ≥1.80 IU/kg or were treated with oral antidiabetic agents; were unaware of or had recurrent severe hypoglycemia; had a significant concomitant illness judged to interfere with the trial (i.e., endocrine, hepatic, renal, cardiac, or neurological disease); were pregnant or intended to become pregnant; or had a suspected allergy to the trial products. Subjects were withdrawn if they became pregnant, did not comply with trial procedures, or if safety concerns were raised.

Treatment

Between the screening visit and the first treatment period, subjects were on their usual basal/bolus regimen. In one treatment period, insulin aspart had to be injected immediately before meals (IAsp pre). In the other treatment period, insulin aspart had to be injected immediately after finishing meals, but not later than 30 min after the start of meals (IAsp post). Subjects were equally randomized to the sequence IAsp pre/IAsp post and IAsp post/IAsp pre.

The insulin aspart had to be used at least three times a day and was the only rapid/short-acting insulin allowed during the treatment periods of the trial. At the beginning of each treatment period, the insulin dose was determined by the dose and frequency of short-acting insulin at randomization. During each treatment period, the dose was to be adjusted according to blood glucose measurements, targeting a fasting/preprandial/nighttime blood glucose concentration of 5–8 mmol/l and a postprandial (1–3 h after meal) blood glucose concentration of <10 mmol/l.

In addition to insulin aspart, the subjects had to continue their pretrial dose regimen of long-acting basal insulin (e.g., NPH, lente, or ultralente) as part of their basal/bolus regimen.

Assessments

Overall blood glucose control was assessed by fructosamine and HbA_{1c} levels before and after each treatment period (visits 1, 3, and 4). Furthermore, glycemic control was assessed by point values and derived parameters (average blood glucose, width of range, and postprandial increment) from seven-point blood glucose profiles (before and 120 min after each meal and at 10:00 P.M. ± 1 h) based on home blood glucose measurements at 1 day within the week before visits 2, 3, and 4.

Safety was assessed by adverse events (AEs) and hypoglycemic episodes reported during the trial, as well as hematological and biochemical laboratory parameters, blood pressure, weight, and physical examination. Hypoglycemic episodes were classified as major (if third party help was required), minor (if blood glucose <3.9 mmol/l was observed and handled by the subject himself/herself), and hypoglycemic symptoms only (if symptoms of hypoglycemia were not confirmed by blood glucose measurement). Treatment satisfaction was assessed by the World Health Organization Diabetes Treatment Satisfaction Questionnaire (DTSQ) (10) completed by adolescents and parents of the children at the clinic before and after each treatment period.

Analysis of fructosamine, HbA_{1c} (National Glycohemoglobin Standardization Program certified method, thus comparable with Diabetes Control and Complications Trial values), hematology, biochemistry, and pregnancy tests were carried out at a central laboratory (Clinserve, Laboratory Hamburg, Hamburg, Germany) using standard enzymatic methods. At home, full blood glucose measurements for the seven-point blood glucose profiles were measured using the One Touch Profile (LifeScan, Milpitas, CA).

Statistical analyses

The trial was designed to have 80% power to detect a tolerable level of inferiority of 10% (i.e., 0.1 on a log scale) for the primary parameter of serum fructosamine levels over the 6-week treatment period.

Efficacy analyses were based on subjects from the intention-to-treat population (all subjects exposed to trial drug) with available data from both treatment periods. Additional efficacy analyses were performed on serum fructosamine and HbA_{1c} based on the per protocol (PP) population, defined as all subjects completing the trial in accordance with the protocol. Subjects were not included in the PP population if they had started treatment with oral hypoglycemic agents,

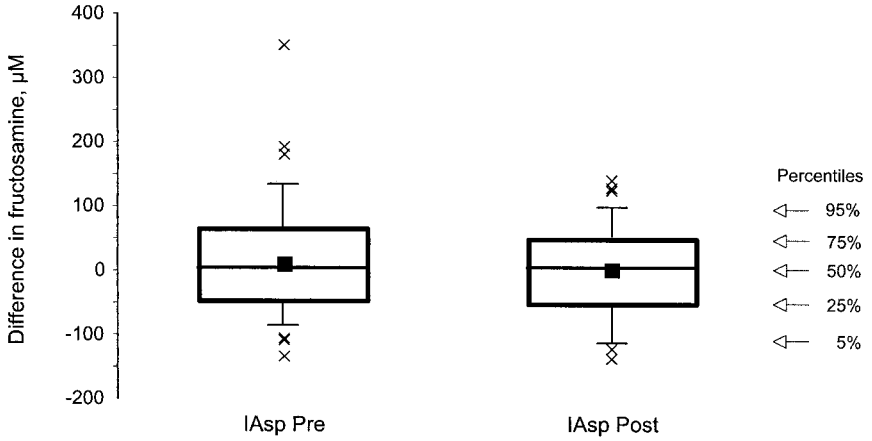

Figure 1—*Difference in fructosamine level after IAsp pre or IAsp post treatment with insulin aspart* (boxes*: 25th, 50th, and 75th percentiles;* bars*: 5th and 95th percentiles; ×, outliers; ■, means). Upper CI level, 0.03 < 0.1 (tolerable level of inferiority).

nontrial short-acting or premixed insulin, discontinued treatment for >5 consecutive days, or otherwise seriously violated the trial protocol. Safety analyses were based on the intention-to-treat population.

Serum fructosamine was analyzed by a one-sided noninferiority test, applying a mixed linear model with treatment, stratum (children or adolescent group), period, sequence, treatment by stratum as fixed effects, and an upper confidence interval (CI) limit of 95%. Similar models were applied for HbA_{1c} and seven-point blood glucose profiles but with an equality hypothesis and two-sided tests. Safety parameters were analyzed by a signed rank test (hypoglycemic episodes, hematology, biochemistry, and DTSQ), McNemar's test (major hypoglycemic episodes), Student's *t* test (weight), and summary statistics (AEs). Transformation was only applied for serum fructosamine (ln transformation). Statistical analyses were performed using SAS version 6.12 on a UNIX platform (SAS Institute, Cary, NC).

RESULTS

Subjects

A total of 76 insulin-treated children (n = 42) and adolescents (n = 34) with type 1 diabetes aged (mean ± SD) 12.2 ± 2.8 years, with BMI 19.9 ± 3.0 kg/m^2 and HbA_{1c} 7.9 ± 1.2% (range 4.7%–11.4%) participated in the trial. Duration of type 1 diabetes was 4.4 ± 2.2 years, and 37 (49%) were boys. Three subjects discontinued the trial prematurely: one due to an increased number of hypoglycemic episodes (IAsp pre), one due to withdrawal of consent (IAsp pre), and one due to vacation (IAsp post). Of the 73 subjects completing the trial, 71 fulfilled the criteria for inclusion in the PP population (2 subjects were excluded due to use of semilente insulin before visits).

Exposure

The mean dose of insulin aspart was similar before and at the end of each treatment period for IAsp post (0.48 ± 0.17 and 0.49 ± 0.19 U · kg^{-1} · day^{-1}) but decreased slightly during IAsp pre (0.50 ± 0.20 and 0.46 ± 0.17 U · kg^{-1} · day^{-1}). Basal insulin dosage was similar between treatments before and at the end of each treatment period: IAsp post (0.45 ± 0.16 and 0.46 ± 0.16 U · kg^{-1} · day^{-1}) as compared with IAsp pre (0.44 ± 0.16 and 0.46 ± 0.17 U · kg^{-1} · day^{-1}). Also, the total daily insulin dose ranges (insulin aspart and basal insulin) were comparable between treatment groups: 0.43–1.70 U · kg^{-1} · day^{-1} for IAsp post and 0.39–1.70 U · kg^{-1} · day^{-1} for IAsp pre.

Pharmacodynamic results

Overall glycemic control as assessed by change in fructosamine level during treatment was noninferior with IAsp post (383.5 ± 83.3 to 385.4 ± 77.3 µmol/l) compared with IAsp pre (366.8 ± 73.7 to 378.0 ± 89.7 µmol/l) as the upper CI limit for the estimated mean difference (ln transformed) between treatments did not exceed the tolerable level of inferiority (95% CI = 0.03 < tolerable level of inferiority = 0.1). Likewise, analysis of change in HbA_{1c} did not reveal any statistically significant difference (P = 0.143) between IAsp pre (7.9 ± 1.3 to 8.0 ± 1.5%) and IAsp post (8.0 ± 1.4 to 8.3 ± 1.5%). The analyses accounted for any variation originating from period and treatment effect. Further examination of the results indicated that this was due to a smaller increase in the mean fructosamine level during the IAsp post sequence compared with IAsp pre (Fig. 1).

The only statistically significant finding from the seven-point blood glucose profiles and derived parameters was a lower postprandial glucose level 120 min after breakfast for IAsp pre as compared with IAsp post (−2.08 ± 0.74 mmol/l, P = 0.016) (Fig. 2). However, borderline significance was reached for the difference between IAsp pre and IAsp post in average blood glucose concentration after each treatment period (−0.71 ± 0.33 mmol/l; P = 0.08).

Safety

During the trial, 50 AEs were reported by 33 subjects (43%) on IAsp pre, and 59 AEs were reported by 38 subjects (51%) on IAsp post. None of the AEs were serious. One subject experienced an AE (headache) rated as probably related to IAsp pre, and three subjects reported AEs (headache, abdominal pain, and otitis media) rated as probably related to IAsp post.

Overall, 995 hypoglycemic episodes occurred during the treatment periods: 544 with IAsp pre and 451 with IAsp post. The majority of episodes were minor (979) or symptomatic (13), and only 3 major hypoglycemic episodes occurred: 2 with IAsp pre and 1 with IAsp post. No statistically significant differences between treatments were found for number, rate, or relative risk (total number, daytime, and nighttime) of hypoglycemic episodes (P > 0.05). Furthermore, the rate of hypoglycemic episodes declined over time for both treatments: IAsp pre (from 1.36 to 0.99 episodes/week) and IAsp post (from 1.23 to 0.86 episodes/week).

There were no clinically relevant abnormalities in laboratory parameters, blood pressure, weight, or physical examination. Although statistically significant differences were found for a few of the laboratory parameters (alanin-aminotransferase, total protein, creatinine, and potassium) and in systolic blood pres-

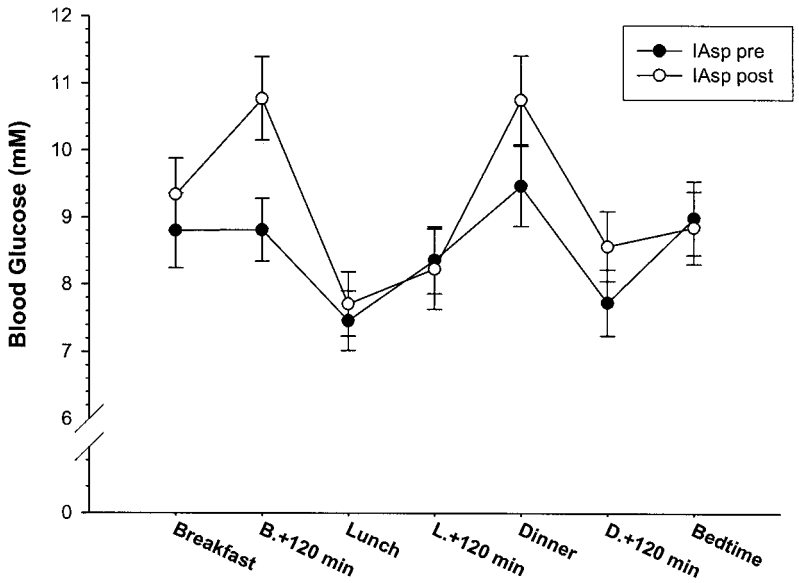

Figure 2—*Seven-point blood glucose profiles for IAsp pre and IAsp post treatment.*

sure, these were only marginal and not considered clinically relevant.

Treatment satisfaction

Total scores on the treatment satisfaction questionnaire were comparable between treatments for parents ($P = 0.12$) and adolescents ($P = 0.15$), and no differences were found for the individual questions in the adolescent group (*P* value range 0.17–0.96). However, among the parents a statistically significant difference ($P = 0.01$) was found in favor of IAsp pre compared with IAsp post for the question, "Would you recommend the form of insulin treatment your child receives to someone else?" (Table 1).

CONCLUSIONS — The present study demonstrates the feasibility of mealtime dosing of insulin aspart without compromising glycemic control in children and adolescents with diabetes. Both currently available rapid analogues (insulin aspart and insulin lispro) have been shown to provide lower postprandial glucose levels than regular human insulin in pediatric patients (7,11). In the present trial, 76 children and adolescents with type 1 diabetes (age 6–17 years) injected insulin aspart preprandially for 6 weeks and postprandially for another 6 weeks in random order. The primary efficacy endpoint was the change of the fructosamine level (an indicator of the glycemic control of the preceding 1–3 weeks). Compared with the baseline concentrations, fructosamine showed a slight increase of 3% (11 μmol/l) under IAsp pre, whereas it remained nearly unchanged under IAsp post. This change relative to baseline under postprandial use of insulin aspart was found to be statistically noninferior when compared with preprandial use. In contrast to what might have been expected from the apparent age effects in the pharmacokinetic studies (7), no clinically relevant differences were found between the two age-groups in any of the parameters studied in the present study.

The incidence of drug-related AEs was very low with both treatment regimens. In particular, no drug-related allergic reactions were observed during the trial. The relative risk for hypoglycemia was not increased by the postprandial injection. In general, the rapid-acting insulin analogues are less likely to induce hypoglycemia than human insulin due to their shorter duration of action (12). This may be especially relevant in the pediatric population where the activities are less predictable than in adults.

In the present study, the glycemic control achieved with both treatment regimens was additionally assessed by the HbA_{1c} and blood glucose levels. HbA_{1c} levels remained at mean levels of ~8%

Table 1—*Analysis of treatment satisfaction scores from parents*

Item	IAsp pre		IAsp post				Pre to post (95% CI)	*P* value
	n	Mean	*n*	Mean	*n*	Mean		
1. How satisfied are you with the insulin treatment your child receives?	71	5.11	72	4.79	69	0.36	(−0.03 to 0.75)	0.09
2. How often have you felt that blood sugars of your child have been unacceptably high?	71	2.48	71	2.68	68	−0.24	(−0.65 to 0.18)	0.33
3. How often have you felt that blood sugars of your child have been unacceptably low?	69	2.28	72	2.07	67	0.18	(−0.23 to 0.59)	0.41
4. How do you feel the general health of your child is?	71	5.44	73	5.25	70	0.19	(−0.14 to 0.51)	0.30
5. To what extent do you feel that diabetes affects the school/social activities of your child?	71	4.41	73	4.45	70	−0.06	(−0.40 to 0.28)	0.81
6. Would you recommend the form of insulin treatment your child receives to someone else?	71	5.39	73	4.86	70	0.49	(0.11 to 0.86)	0.01
7. How satisfied would you be to continue your child's present form of insulin treatment?	71	5.14	73	4.86	70	0.24	(−0.13 to 0.62)	0.30
Treatment satisfaction score	71	25.49	72	24.26	69	1.23	(−0.03 to 2.49)	0.12

SEM ranged from 0.01 to 0.18 for the individual questions. For the overall treatment satisfaction score, the SEMs were 0.44 for IAsp pre vs. 0.58 for IAsp post.

with both preprandial and postprandial use of insulin aspart, thus supporting the findings for fructosamine. However, being an indicator of glycemic control beyond the duration of each treatment period (6 weeks), the HbA_{1c} levels after each treatment period cannot exclusively be ascribed to the preceding treatment period but is possibly also influenced by a carryover effect from previous treatment (pretrial or comparator treatment, dependent on the treatment sequence). The seven-point blood glucose profile indicated a tendency toward higher levels when insulin aspart is injected postprandially, but these differences were not significant. The finding of a higher-after-breakfast and, to a smaller extent, higher-after-dinner blood glucose level during treatment with postprandial insulin analogues is in agreement with recent findings investigating the glucose profiles in adolescents with diabetes by means of a continuous blood glucose monitoring device. Compared with adolescents treated with preprandial regular insulin, the daytime glucose profiles revealed insufficient meal-related insulin dosing at breakfast and dinner using analogues postprandially (13).

Now that this study demonstrates the feasibility of this therapeutic principle of postprandial administration of insulin aspart, future studies need to look at strategies to optimize postprandial dosing in the pediatric population. In the present study, changes to basal insulin supply or dosing algorithms tailored for postprandial injection based on meal size and composition were not intended. This may have prevented an improvement in glycemic control.

The results of this study are in agreement with studies in adults with type 1 diabetes where pre- and postprandial injection appeared to be comparable when studying either of the two available rapid-acting analogues, insulin aspart (14) and insulin lispro (15). In a small trial in toddlers, postprandial analogue injection was successfully applied in the very young (16). Some (1,17,18) but not all studies (19) in adults have shown significant improvements in HbA_{1c} using rapid-acting analogues, indicating the need for adjusting the basal insulin supply adequately to achieve good glycemic control (20). However, in one trial using insulin aspart, the improvement in HbA_{1c} remained significant even after adjustment for differences in NPH dosing (1). Trials using insulin aspart (21) and insulin lispro (22) in subcutaneous infusions in adults have shown maintained or even improved HbA_{1c} (23,24) and a tendency toward improved postprandial glycemic control with no increase in hypoglycemia compared with conventional therapy. Such studies in the pediatric population are currently lacking.

Adolescents and their parents expressed a high level of treatment satisfaction for both treatment regimens. The ratings for postprandial application did not differ significantly from the ones for preprandial application. Thus, a notably higher satisfaction with the postprandial administration was not observed in the present trial. Surprisingly, parents were in general found to be reluctant to recommend postprandial injection to others. As can be seen in the decline of hypoglycemic events over time, a learning curve has to be expected using this new therapeutic principle. When attempting to elucidate this finding, after the study, it was mentioned by patients and parents alike that it took some time to get used to postprandial injection after years of taking insulin before meals and that the postprandial injection was simply forgotten in some instances. In addition to a feeling of less opportunity for parental supervision during postprandial injection, the risk for accidental insulin omission may have contributed to the parents' apprehension toward a new therapeutic principle for their children.

From the results of the present trial, it can be concluded that insulin aspart was shown to be very safe with both treatment regimens. Thus, postprandial administration of insulin aspart is a feasible and effective alternative to preprandial administration for children and adolescents when increased flexibility in timing of injections and the opportunity of dose adjustment according to meal size and composition is needed. However, the tendency to higher blood glucose levels 2 h after the meal with postprandial injection indicates that preprandial injection is preferable when the meal size can be predicted accurately. Future studies need to look at changes in the overall therapeutic regimen that may eventually lead to improved glycemic control with postprandial insulin analogue injection.

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