Improved Postprandial Glycemic Control With Insulin Aspart

A randomized double-blind cross-over trial in type 1 diabetes

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OBJECTIVE — Insulin aspart is a novel rapid-acting insulin analog. This study was performed to compare the postprandial serum glucose control after administration of insulin aspart with that of unmodified human insulin.

RESEARCH DESIGN AND METHODS — The trial was a double-blind double–dummy injection three-way cross-over study in 22 subjects with type 1 diabetes. Insulin aspart was injected subcutaneously immediately before the meal, and human insulin was injected subcutaneously 30 min before the meal or immediately before the meal.

RESULTS — The postprandial glucose control as assessed by the excursion of serum glucose was superior with insulin aspart as compared with that with human insulin injected immediately before or 30 min before a meal (891 ± 521 vs. 1,311 ± 512 vs. 1,106 ± 571 mmol · l^{-1} · min^{-1}, $P < 0.0001$ and $P < 0.02$). This was accompanied by a significantly lower glucose maximum concentration [$C_{max(SG)}$] for insulin aspart than for human insulin injected immediately before the meal (13.5 ± 3.5 vs. 16.4 ± 3.4 mmol/l, $P < 0.001$). Insulin aspart was, on average, absorbed twice as fast as human insulin, with median time to insulin aspart $C_{max(ins)}$ on the order of 40 min, and the maximum concentration was approximately twice as high for insulin aspart. The relative bioavailability of the insulins indicated a similar extent of absorption. Insulin aspart was well tolerated.

CONCLUSIONS — This study demonstrates the ability of insulin aspart to improve postprandial glucose control when compared with human insulin.

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There is a need to improve insulin delivery in the treatment of diabetes. The Diabetes Control and Complications Trial has confirmed the link between glucose regulation as assessed by HbA_{1c} and prevention of late complications of diabetes (1–4). To achieve optimal control of blood glucose, unmodified human insulin may be administered before each main meal in combination with an intermediate-acting insulin for nighttime control, which is the meal-related treatment regimen (5).

In healthy individuals, ingestion of food causes a rise in serum insulin to maximum concentration after 30–45 min, followed by a 2- to 3-h decline to basal levels. By contrast, subcutaneous injection of human insulin causes a slow increase in serum insulin to achieve maximum concentration after 1–2 h following the injection (6–9). Furthermore, the duration of the injected insulin is longer than desired, and the return to baseline occurs after 6–8 h. The net effect of subcutaneous injection in a patient with diabetes is early postprandial hyperglycemia followed by a risk of hypoglycemia before the next meal or in the middle of the night. To counteract the slow absorption of human insulin, it is recommended that human insulin be injected 30 min before a meal.

The rate-limiting step in the absorption of human insulin is a hexamer formation at high concentrations of human insulin such as those obtained in the injectable fluid (10,11). The hexamers slowly dissociate before absorption to the bloodstream occurs. Brange et al. (11) found that by replacing certain amino acids in the insulin molecule, the tendency to self-associate could be reduced without affecting the insulin-receptor kinetics. One such insulin analog is insulin aspart, in which aspartic acid has been substituted for the amino acid proline at the B28 position. Preclinical studies of insulin aspart have indicated that receptor interaction kinetics to the insulin receptor and to the IGF-1 receptor are equivalent to that obtained with human insulin (12).

Previous clinical studies have characterized the pharmacokinetics of insulin aspart in healthy volunteers and in patients with diabetes. The pharmacokinetic studies have shown a faster absorption and faster effect compared with human insulin (13–16). One study demonstrated an equivalent metabolic effect after intravenous administration of insulin aspart or human insulin (17).

The present study was the first double-blind study undertaken to compare the postprandial glycemic control of insulin aspart administered immediately before a meal with that of human insulin administered 30 min before a meal or immediately before a meal in subjects with type 1 diabetes.

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Abbreviations: AUC, area under the curve; $C_{max(ins)}$, maximum insulin concentration; $C_{max(SG)}$, maximum serum glucose concentration; $EXC_{(SG)}$, total baseline-corrected excursion of serum glucose; $MRT_{(ins)}$, mean residence time of insulin; $t_{max(ins)}$, time of maximum insulin concentration; $t_{max(SG)}$, time of maximum serum glucose concentration.

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

RESEARCH DESIGN AND METHODS

Subjects

A total of 24 adult male subjects with type 1 diabetes were enrolled in the trial after giving signed informed consent. The subjects were recruited from the patient pool in the Tayside and Grampian regions of Scotland. The subjects had type 1 diabetes of at least 2 years' duration, were currently on a meal-related treatment regimen with a combination of NPH insulin and soluble human insulin, presented with a meal-stimulated C-peptide of <0.1 nmol/l at 1–3 h postmeal, and were reasonably well-controlled as assessed by an HbA_{1c} of <9.0%. Of the 24 enrolled subjects, 22 completed the study and 2 were withdrawn, 1 for personal reasons and 1 for adverse events. The study was approved by the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Design

This was a single-center double-blind double-dummy randomized three-way crossover trial. There were three study days, separated by at least a week. On each study day, the subjects received two injections, one 30 min before and one immediately before a standard breakfast. One of the injections was placebo, and the other injection was insulin aspart 0.15 U/kg body wt (only immediately before the meal) or unmodified human insulin (Actrapid; Novo Nordisk A/S, Bagsvaerd, Denmark) 0.15 U/kg body wt (30 min before the meal or immediately before the meal). The test drugs or placebo were supplied in cartridges and administered by a pen device (NovoPen 1.5; Novo Nordisk).

Study day procedure

The subjects were admitted to the clinic on the evening before the test. On that evening, no NPH insulin was allowed. The subjects received an overnight euglycemic clamp by means of a human insulin infusion aiming at a target blood glucose level of 5–8 mmol/l. The study day was only performed if this target level was reached in the morning.

In the morning, subcutaneous injections were given 30 min before and immediately before a standard breakfast of 535 kcal. The injections were given midway between the umbilicus and the anterior superior iliac spine, alternating right and left sides, by raising a skin-fold and injecting at 45° to the skin. Blood sampling for serum glucose and serum insulin was performed at –30 min and immediately before the meal (before the injections), and at 10, 20, 30, 40, 50, 60, 70, 80, 90, 105, 120, 150, 180, 210, 240, 270, 300, and 360 min after start of the meal.

Table 1—*Subject characteristics*

Age (years)	33.2 ± 8.6
Height (m)	1.76 ± 0.09
BMI (kg/m²)	25.1 ± 2.3
Duration of diabetes (years)	11.4 ± 7.1
HbA_{1c} (%)	7.6 ± 1.1

Data are means ± SD. n = 24. The upper normal limit of HbA_{1c} is 6.2%.

Pharmacokinetic and pharmacodynamic end points

The primary endpoint was defined as the total baseline-corrected excursion of serum glucose from 0 to 240 min [$EXC_{(SG)}$]. This was calculated as the sum of the area under the curve above baseline serum glucose plus the area above the curve below baseline serum glucose. The secondary end points derived from the serum glucose profiles from 0 to 240 min were as follows: maximum serum glucose concentration [$C_{max(SG)}$] and time of maximum serum glucose concentration [$t_{max(SG)}$] during the time interval from $t_{max(SG)}$ to 240 min. The secondary end points derived from the insulin profiles from 0 to 360 min or –30 to 330 min were as follows: mean residence time [$MRT_{(ins)}$], maximum insulin concentration [$C_{max(ins)}$], time of maximum insulin concentration [$t_{max(ins)}$] and area under the insulin concentration time curve [$AUC_{0–6h(ins)}$] as assessed by the trapezoidal rule.

Mean residence time (MRT) was calculated as area under the moment curve [$AUMC_{0–6h(ins)}$] divided by $AUC_{0–6h(ins)}$ for the insulin profiles. $AUC_{0–\infty(ins)}$ was estimated using the equation $AUC_{0–\infty} = AUC_{0–tn} + \hat{C}_n/\hat{\lambda}_z$, where $\hat{C}_n$ is the estimated concentration at the last sampling time point, t_n, and $\hat{\lambda}_z$ is the terminal elimination rate constant derived from the slope of the terminal linear part of the ln(concentration) versus time curve.

The relative bioavailability of insulin aspart versus human insulin was derived as the ratio

$$F(AUC) = \frac{AUC_{0–\infty(IAsp)}}{AUC_{0–\infty(HI)}}.$$

Biochemical analysis

Serum human insulin and insulin aspart concentrations were assayed using a commercial radioimmunoassay kit (Pharmacia, Uppsala, Sweden) validated for both insulins at concentrations below 600 pmol/l. The Pharmacia Insulin RIA 100 does not measure the concentration of insulin aspart proportionally to human insulin concentrations. Therefore, the following correction formula was used to calculate the correct insulin aspart concentration in serum: $\text{Insulin aspart}_{corrected} = F \times$

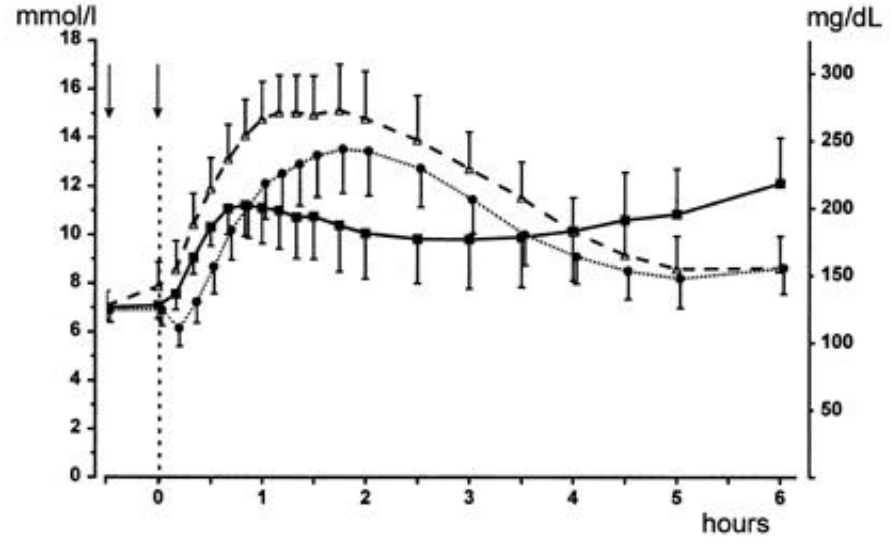

Figure 1—*Mean postprandial serum glucose profile in 22 subjects with type 1 diabetes after injection of insulin aspart (■—), human insulin immediately before the meal (△– –), or human insulin 30 min before the meal (●· · ·). The two arrows indicate subcutaneous injection times, and the vertical dotted line indicates the time of meal.*

Table 2—*Derived pharmacodynamic and pharmacokinetic parameters from the serum glucose and insulin profiles obtained with insulin aspart and human insulin*

	Insulin aspart	Human insulin	
		t = 0	t = 230
Pharmacodynamics			
$EXC_{(SG)}$			
(mmol · l^{-1} · min^{-1})	891 ± 521	1,311 ± 512	1,106 ± 571
Estimate		0.64 (0.52 to 0.78)	0.78 (0.63 to 0.95)
P value		<0.0001	<0.02
$C_{max(SG)}$			
(mmol/l)	13.5 ± 3.5	16.4 ± 3.4	14.5 ± 3.5
Estimate		0.82 (0.74 to 0.91)	0.93 (0.84 to 1.04)
P value		<0.001	NS
$t_{max(SG)}$			
(min)	60 (40-150)	105 (60-120)	105 (105-120)
Estimate		−15.0 (−40.0 to 30.0)	−32.5 (−55.0 to 17.5)
P value		NS	NS
Pharmacokinetics			
$C_{max(ins)}$			
(pmol/l)	493 ± 257	215 ± 121	239 ± 131
Estimate		2.27 (2.04 to 2.53)	2.04 (1.83 to 2.27)
P value		<0.0001	<0.0001
$t_{max(ins)}$			
(min)	40 (30–40)	97.5 (70–150)	80 (30–120)
Estimate		−60.0 (−80.0 to −40.0)	−42.5 (−70.0 to −20.0)
P value		<0.0001	<0.002
$AUC_{0–6h(ins)}$			
(nmol · l^{-1} · min^{-1})	71.0 ± 39.6	52.9 ± 29.6	56.6 ± 29.7
Estimate		1.33 (1.24 to 1.42)	1.23 (1.15 to 1.32)
P value		<0.0001	<0.0001
$AUC_{0–\infty(ins)}$			
(nmol · l^{-1} · min^{-1})	86.0 ± 61.2	111.3 ± 106.8	97.8 ± 83.1
Estimate		0.87 (0.72 to 1.04)	0.92 (0.76 to 1.11)
P value		NS	NS
$MRT_{0–6h(ins)}$			
(min)	122 ± 17.6	162 ± 18.8	153 ± 15.6
Estimate		0.75 (0.72 to 0.78)	0.79 (0.76 to 0.83)
P value		<0.0001	<0.0001

Data are means ± SD or median (95% CI). The estimates (ratio or difference) and 95% CIs refer to comparison between insulin aspart and human insulin at t = 0 or t = 230 min.

(1,503 × insulin aspart$_{fraction}$)/(1,398 − insulin aspart$_{fraction}$), where F denotes the dilution factor and insulin aspart$_{fraction}$ is given in pmol/l as diluted assay results.

Serum glucose, drugs-of-abuse screen, and a standard biochemical and hematological clinical profile were measured before and after the study and assayed by standard methods.

Statistical analysis

The primary efficacy assessment was the postprandial $EXC_{(SG)}$. Assuming an intrapatient coefficient of variation for $EXC_{(SG)}$ of up to ~1.67 mmol · l^{-1} · min^{-1}, and using a significance level of 5%, a sample size of 21 would detect a true difference (ratio of the clinically significant difference/intrapatient SD) of 1.0 (10%/10%) with the required certainty (power >90%). This is consistent with previous experience of this kind of study in type 1 diabetes. All the tests were two tailed, and the significance level was set as 5% for all analyses. Efficacy results are presented using the per-protocol population. Statistical analyses were made using SAS for UNIX version 6.09 (SAS Institute, Cary, NC).

All end points were analyzed by analysis of variance with subject as random effect and treatment as a fixed effect. Statistical analysis of all end points, except t_{max}, were performed on log-transformed values to correct skewed distributions. The analysis of t_{max} was based on pair-wise treatment comparisons using Wilcoxon signed-rank test, for which the Hodges-Lehmann estimate and a nonparametric 95% CI for the estimate was constructed. Results are presented as mean ± SD unless otherwise specified.

RESULTS

Subjects and medication

Table 1 displays the characteristics of the 24 participating subjects. The mean daily insulin dose at study entry was 0.69 ± 0.20 U/kg body wt (ranging from 0.34 to 1.18 U/kg). The study test dose (0.15 U/kg) ranged from 9 to 13 units.

Pharmacodynamic response

The $EXC_{(SG)}$ was significantly lower for insulin aspart than for either of the human insulin administrations ($P < 0.0001$ and $P < 0.02$) (Fig. 1, Table 2). $C_{max(SG)}$ was significantly lower for insulin aspart than for human insulin injected at t = 0 min ($P < 0.001$) but not different from human insulin injected at t = –30 min. The shorter duration of action of insulin aspart is clearly visible on the graph and the curves, with an intercept at 3.5 to 4 h.

Pharmacokinetics

As visualized in Fig. 2, the pharmacokinetics of insulin aspart clearly differed from those of human insulin, as demonstrated by the doubling of the maximum concentration ($P < 0.0001$) and by a time to maximum concentration twice as fast as for human insulin ($P < 0.0001$ and $P < 0.002$, Table 2).

The residence time of insulin aspart in the circulation is reflected in the MRT, which was statistically significantly much shorter with insulin aspart than with human insulin ($P < 0.0001$). The $AUC_{0–6h(ins)}$ of insulin aspart was larger than that of human insulin ($P < 0.0001$). However, because of the faster absorption and thus faster elimination of insulin aspart from the circulation, the $AUC_{0–\infty(ins)}$ was not significantly different from that of human insulin. Thus, assuming similar clearance rates, there was no difference in the relative bioavailability of insulin aspart compared with human insulin.

Safety

All adverse events were mild or moderate in severity. Of the 24 subjects exposed to

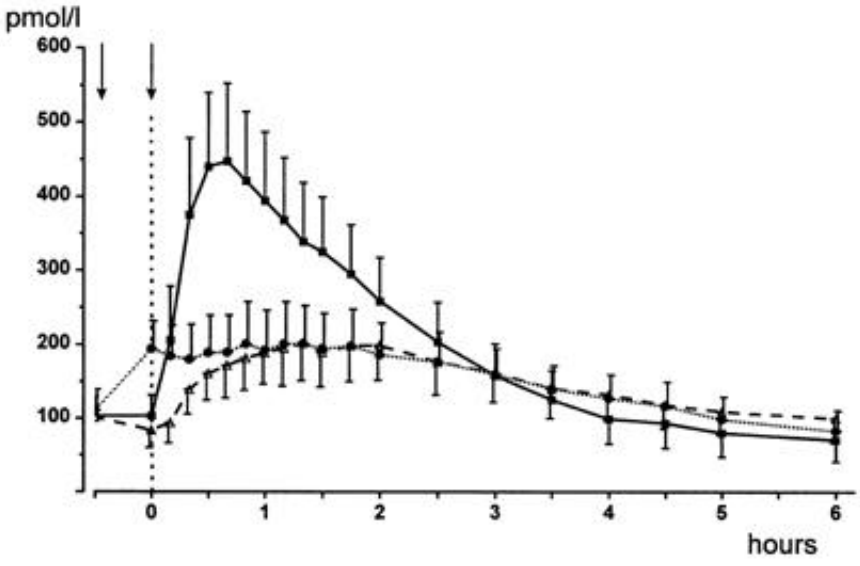

Figure 2—*Mean postprandial serum insulin profiles in 22 subjects with type 1 diabetes after injection of insulin aspart (■—), human insulin immediately before the meal (△– –), or human insulin 30 min before the meal (●· · ·). The two arrows indicate subcutaneous injection times, and the vertical dotted line indicates the time of meal.*

insulin aspart, 14 had 30 adverse events. Of the 23 subjects exposed to human insulin$_{t=0}$, 15 had 25 adverse events; and of the 22 subjects exposed to human insulin$_{t=-30}$, 11 had 17 adverse events. The most common adverse events were hypoglycemia (9 events with insulin aspart, 8 events with human insulin$_{t=0}$, and 9 events with human insulin$_{t=-30}$) and headache (6 events with insulin aspart, 5 events with human insulin$_{t=0}$, and 2 events with human insulin$_{t=-30}$). All these events were mild to moderate in severity and were spontaneously resolved. One subject was withdrawn before study day 3 because of cough and cold. There were no clinically significant abnormalities in the biochemical or hematological profiles or in vital signs.

CONCLUSIONS — Several conclusions emanate from observations made in the present study. Insulin aspart demonstrated the ability to improve postprandial glucose control over human insulin. The study design was quite rigorous, with double-blind double-dummy injections and with meals standardized with respect to quantity and composition. Human insulin is recommended to be injected 30 min before the meal to allow for absorption in time for the meal (6–9). Insulin aspart improved postprandial glucose control not only as compared with human insulin injected immediately before the meal but also as compared with human insulin injected 30 min before the meal.

The short duration of action of insulin aspart is both an advantage and a disadvantage. On the one hand, it allows better control of early postprandial hyperglycemia. On the other hand, it may be insufficient for control of late postprandial glucose resulting in increased preprandial glucose values before the next meal, as has already been noted with another rapid-acting insulin analog, insulin lispro (18). One way to improve late postprandial control could be to add intermediate or long-acting insulin both morning and evening. In fact, such twice-daily NPH insulin regimens are already common with human insulin, especially in patients in whom the time between the main meals is long: such an example is patients in southern Europe where a majority of patients take NPH insulin more than once daily.

The present study also confirms that postprandial serum glucose control is better when human insulin is injected as recommended, namely 30 min before a meal rather than immediately before the meal. Unfortunately, empirical observations indicate that many patients with diabetes do not adhere to this guideline but inject immediately before a meal, partly because of fear of hypoglycemia before the meal and partly because of practical difficulty with planning (19–22) or convenience. Immediate preprandial injection with insulin aspart may not only improve postprandial glucose control but may also relieve patients from the guilt of not medicating as prescribed by the physician. Thus, there is reason to speculate that the quality of life and the patient-doctor relationship may be improved in certain patients. However, this needs clinical confirmation.

The primary efficacy parameter in the present trial is excursion of serum glucose. The excursion is in reality a baseline-corrected area under the concentration time curve (AUC). An advantage of using the excursion rather than a time point fixed in relation to the meal is that the excursion takes the whole time period into account. Furthermore, premeal baseline serum glucose shows variation even when attempts are made to minimize these day-to-day variations with continuous intravenous insulin administration. Therefore, the baseline-corrected excursion is a preferable measure of the drug-related effect over the use of a standard AUC.

The pharmacokinetic profile of insulin aspart was quite different from that of human insulin and was the underlying reason for the difference in the pharmacodynamic effect. The most striking finding was the rapid and sharp rise in serum insulin concentration to a level approximately twice that of human insulin. Furthermore, the residence time of insulin aspart as assessed by MRT was significantly reduced compared with that of human insulin.

As shown in Table 2, the estimate of the difference in $AUC_{0–6h}$ of insulin aspart was 33 and 23% greater than those of the two human insulin AUCs, respectively. This can be attributed to the fact that a substantial proportion of the AUC of human insulin lies after the 6-h time point. When extrapolating to infinite time, similar AUCs and similar bioavailability of insulin aspart was found relative to human insulin, which is supported by data in healthy volunteers (23). The comparison of bioavailability assumes similar clearance rates of insulin aspart and human insulin, which has recently been confirmed for insulin aspart (N.D. Harris, unpublished observations).

It is tempting to compare the results of the current trial with those of insulin lispro from the published literature. For example, in a comparable trial, Torlone et al. (24) found a mean insulin lispro C_{max} of 393 pmol/l at a mean of 41 min in 10 subjects with type 1 diabetes after a dose of 0.15 U/kg. These data indicate pharmacokinetics similar to those of insulin aspart in the

current trial. However, a comparison in pharmacodynamic response cannot be performed with published data because of differences in glucose load administered with the meal and differences in study design.

In conclusion, the present study demonstrates the ability of insulin aspart to improve postprandial serum glucose in subjects with type 1 diabetes. The novel rapid-acting insulin analog may be a means of improving overall glycemic control in subjects on a meal-related treatment regimen. In light of these findings, studies are presently underway to evaluate long-term metabolic control with insulin aspart.

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