Optimal Provision of Daytime NPH Insulin in Patients Using the Insulin Analog Lispro

ABU BAKER E. AHMED, MRCP
PHILIP D. HOME, DM, DPHIL, FRCP

OBJECTIVE — Insulin lispro improves early postprandial blood glucose control but can result in late interprandial hyperglycemia. As an approach to resolving this problem, we performed a randomized, crossover study with four treatment arms, comparing the daytime metabolic profile after either premeal lispro alone or premeal lispro with optimal daytime NPH insulin and with standard human regular insulin.

RESEARCH DESIGN AND METHODS — Twelve C-peptide negative type 1 diabetic patients were studied on four separate study days, at least 7 days apart. On each study day, patients received one of the four study insulin treatments, in random order, with identical meals and snacks. The four treatments were 1) premeal human regular insulin before lunch and supper at unchanged dose; 2) premeal lispro (unchanged dose) at lunchtime and dinner; 3) prelunch reduced-dose lispro (70%) before lunch and supper with supplemental lunchtime NPH and with a 6-h interval until dinner; and 4) pre-lunch reduced-dose lispro (70%) before lunch and supper with supplemental lunchtime NPH and with a 8-h interval until dinner. All patients were using their usual premeal plus basal insulin regimen during the period of the study, with human regular insulin before meals and NPH insulin at bedtime.

RESULTS — Postprandial blood glucose concentrations (1230–1500) were lower after reduced or usual lispro dose compared with human regular insulin (5.5 ± 0.2 and 5.6 ± 0.2 vs. 8.2 ± 0.5 mmol/l, $P < 0.001$), with no difference between the lispro doses. However, preprandial (1800) blood glucose levels deteriorated to higher levels after usual-dose lispro alone compared with either human regular insulin ($P < 0.05$) or reduced-dose lispro plus NPH ($P < 0.05$) (8.9 ± 0.3 vs. 7.1 ± 0.8 and 6.4 ± 0.4 mmol/l), with no difference between human regular insulin and reduced-dose lispro plus NPH. During the 2 h between the usual and delayed mealtime, blood glucose concentrations remained controlled on lispro plus NPH (2000: 6.5 ± 0.4 mmol/l).

CONCLUSIONS — Reduced-dose lunchtime lispro plus NPH maintained the improvement in postprandial blood glucose control with no deterioration in interprandial blood glucose control, even up to a late meal.

Diabetes Care 21:1707–1713, 1998

The main objective of intensive insulin therapy is to maintain strict glycemic control in patients with diabetes, since this reduces the risk of long-term diabetic complications (1,2). In multiple-injection therapy, the mealtime insulin requirement is supplied by short-acting unmodified regular insulin aiming to maintain the postprandial blood glucose concentrations as close to normal as possible (3–5). However, the premeal short-acting human regular insulin reaches peak action rather late after subcutaneous injection; consequently, the glucose excursion is often excessive in the early postprandial period, and the hypoglycemic risk is enhanced in the late postprandial period (6–8).

In the last few years, a number of short-acting insulin analogs with improved pharmacokinetic characteristics have been biosynthetically engineered (9–11). One of these is insulin analog lispro (Humalog; Eli Lilly, Indianapolis, IN), which has less of a tendency for self-association in subcutaneous injection site. Therefore, it is absorbed faster after subcutaneous injection than is human regular insulin. As a result, it has a rapid onset and a short duration of action (<4 h) (5,12,13).

Insulin regimens based on insulin lispro achieved improvement in postprandial blood glucose control (14–22), but improvement in overall blood glucose control has proved difficult to demonstrate (18–22). At least in part, this has been shown to be due to higher blood glucose concentrations in the late postprandial period (21–24) and in the early part of the night (17), probably because of the failure of premeal lispro to cover the basal insulin requirement right through to the next meal.

The present study was designed to examine the hypothesis that by dose substitution with basal NPH insulin, patients using short-acting insulin lispro could have good late as well as early postprandial blood glucose control.

Patients using human regular insulin in regimens of mealtime plus basal insulin often take the opportunity to delay the time of the next meal without disturbance of blood glucose control, as has proved to be possible in formal studies (25). Thus, in the present study, we also assessed the metabolic control before a delayed evening meal in patients receiving lispro plus NPH insulin at lunchtime.

RESEARCH DESIGN AND METHODS — This was a four-way, randomized, crossover, open-label, comparative study conducted in type 1 diabetic patients attending a specialist diabetes service.

Table 1—*Patient characteristics*

n	12
Sex (M/F)	7/5
Age (years)	40 ± 14
Weight (kg)	74 ± 15
BMI (kg/m²)	26 ± 3
C-peptide (nmol/l)	0.08 ± 0.05
HbA$_{1c}$ (%)	7.7 ± 0.7
Duration of diabetes (years)	16 ± 11
Total daily insulin dose (U)	51 ± 16

Data are means ± SD.

Patients

Twelve type 1 diabetic patients gave written informed consent to participate in the study, which was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

All patients were normally using a regimen of premeal plus basal insulin, with unmodified human regular insulin before each meal and basal NPH insulin at bedtime. All patients had been stable on insulin for >1 year with a mean HbA$_{1c}$ of 7.7 ± 0.7% (SD) (normal <6.1%) and no serious hypoglycemic events. All patients had serum C-peptide <0.18 nmol/l when blood glucose concentration was >5.0 mmol/l. Patient details are given in Table 1. All were healthy apart from their diabetes and did not have late diabetic complications.

Methods

Each patient was studied on 4 separate days, at a 1- to 4-week interval, in random order. One to 3 weeks before the first study day, patients were screened by medical history, physical examination, blood count, and serum biochemical analysis.

On each study day, the patients were requested to undertake their normal activities and to take their normal food and insulin up to the time of admission to the investigation unit at 1100 for study from 1130 to 2200. Thus, patients had had their usual dose of the prebreakfast human regular insulin on the morning of each study day. A sampling cannula was placed in one arm and kept patent between samples with 0.15 mol/l NaCl in water. Blood glucose concentration was measured on arrival at the investigation unit, and patients whose blood glucose concentrations were not between 4.0 and 12.0 mmol/l at 1130 or whose blood glucose concentrations were >2.5 mmol/l different on study day 2, 3, or 4 from study day 1, were requested to return another day.

Patients had lunch from a choice of foods at 1200 on all four study days. They had an evening meal from a choice of foods at 1800 on three of the study days and were delayed by 2 h to 2000 on one day. The choice and amount of food were recorded, and identical meals and snacks were then given at the same time on all study days. Five minutes before each noon or evening meal, the patient received a subcutaneous injection of the study insulin—insulin analog lispro (Humalog; Eli Lilly) on three of the study days or human regular insulin (Humulin S; Eli Lilly) on the other—into the anterior abdominal wall of the periumbilical region by means of a pen-injector. The schedule of injections was single-blind according to a randomization schedule.

One of a series of four insulin treatments was given on each study day (Table 2). On the control study day, patients had their lunch and evening meal at the usual mealtime, 1200 and 1800, respectively. They received human regular insulin before lunch (10 ± 5 U; mean ± SD) and before the evening meal (12 ± 5 U), the doses being the same as the patients' usual premeal insulin doses. On another study day, patients received premeal lispro before lunch and the evening meal at their usual mealtime human regular insulin doses with no NPH insulin. On the other two study days, patients received a reduced dose (70%) of lispro before lunch (7 ± 3 U) and the evening meal (9 ± 3 U), a supplemental extended-acting NPH insulin before lunch only, and no NPH insulin before the evening meal. On these two study days, the premeal lispro dose was reduced by 30% of the patient's usual mealtime human regular insulin before each meal, whereas the pre-lunch NPH insulin dose was equivalent to 30% of the patient's usual pre-lunch human regular insulin plus 30% of the usual pre-dinner human regular insulin dose (7 ± 2 U). Total insulin dose was thus unchanged, and the resulting lunchtime lispro:NPH insulin ratio is 50:50. On these two study days, the patients had their lunch at the usual mealtime (1200), but the evening meal was at the usual mealtime (1800) on 1 day and delayed by 2 h to 2000 on the other day (Table 2).

On all study days, patients received the premeal insulin injections 5 min before the meal. This was chosen to correspond to normal patient practice and because of the dangers of earlier injection unless glucose levels have been measured (26–29).

Venous blood samples for measurement of blood glucose, plasma free insulin, and blood intermediary metabolites concentrations were obtained at 1130, every 30 min until 1400, hourly until 1800, every 30 min until 2000, and then hourly until 2200. Bedside blood glucose monitoring was carried out throughout the study using a Yellow Springs Instruments analyzer (see below).

If blood glucose concentration fell to <3.0 mmol/l, blood sampling frequency was increased to every 30 min. Patients were treated for hypoglycemia only if they were symptomatic. Symptomatic hypoglycemia was managed with a 20-g carbohydrate snack, repeated if symptoms did not abate within 10 min.

Biochemical analysis

Blood glucose was measured using a glucose oxidase method (Yellow Springs Instruments Model 2300 STAT PLUS Glucose Analyser, Yellow Springs, OH). Blood glucose was measured in whole venous blood within 2 min of blood sampling. To remove antibody-bound insulin, plasma

Table 2—*Insulin therapy*

Protocol arm	Pre-lunch insulin		Pre-dinner insulin	
	Time	Insulin (dose)	Time	Insulin (dose)
Standard insulin	1155	Human (100%)	1755	Human (100%)
Usual lispro alone	1155	Lispro (100%)	1755	Lispro (100%)
Lispro + NPH + usual-time dinner	1155	Lispro (70%) + NPH (30%)	1755	Lispro (70%) (no NPH)
Lispro + NPH + delayed dinner	1155	Lispro (70%) + NPH (30%)	1955	Lispro (70%) (no NPH)

Table 3—*Blood glucose concentrations (mmol/l)*

	Standard insulin	Usual lispro alone	Lispro + NPH
Baseline (1200)	7.5 ± 0.8	7.4 ± 0.5	7.1 ± 0.7
Postprandial (1230–1500)	8.2 ± 0.5	5.5 ± 0.2†	5.6 ± 0.2†
2-h postprandial (1400)	9.0 ± 1.0	5.4 ± 0.4†	5.5 ± 0.4†
Preprandial (1800)	7.1 ± 0.8‡	8.9 ± 0.3*	6.4 ± 0.4‡
Postprandial (1830–2100)	9.2 ± 0.9	7.1 ± 0.6*	6.6 ± 0.5†
2-h postprandial (2000)	9.5 ± 1.0	6.6 ± 0.7*	5.8 ± 0.5†
Pre-bedtime (2200)	7.9 ± 0.7	7.7 ± 0.7	7.1 ± 0.6

Data are means ± SEM. *$P < 0.05$, †$P < 0.005$ compared with standard human regular insulin; ‡$P < 0.001$ compared with usual-dose lispro alone. Postprandial (1230–1500) and postprandial (1830–2100) show the means of five measurements.

Figure 1—*Daytime blood glucose (mmol/l) (A), plasma free insulin (pmol/l) (B), and blood 3-hydroxybutyrate (μmol/l) (C) concentrations (mean ± SEM) in type 1 diabetic patients after subcutaneous injection of standard premeal unmodified human regular insulin (□); premeal insulin lispro in a usual premeal dose with no NPH (●); or lispro in a reduced dose plus supplemental NPH insulin dose (▲). The meals (lunch and dinner) were at usual times—1200 and 1800, respectively.*

was prepared immediately after venipuncture, mixed with an equal volume of 30% polyetheylene glycol, and centrifuged immediately (30). Plasma free insulin was measured by radioimmunoassay (31), using insulin or lispro standards as appropriate. Blood intermediary metabolites were measured as previously described (32).

Statistical analysis

All data were entered into a computer database and checked for correct entry. Data analysis was by standard parametric methods. Results are expressed as means ± SEM unless stated otherwise. A P value <0.05 was considered statistically significant. The blood glucose concentration at each time point was plotted for the four treatment groups. The preferred method of statistical analysis of the profile is by comparison of mean concentration or area under the concentration curve for predefined periods of interest. Statistical comparisons of the various treatments was by analysis of variance for repeated measures with post hoc application of Student's Newman Keuls test for multiple comparison. Individual pairs of treatment points of interest were analyzed using Student's paired t test.

The blood glucose level for biochemical hypoglycemia was set as <0.3 mmol/l. Biochemical hypoglycemia, with or without symptoms, treated or untreated, was taken as the end point for comparison of incidence of hypoglycemia. Biochemical hypoglycemia was also compared for the predefined periods of interest using McNemar test.

Other results are reported as a matter of observation only.
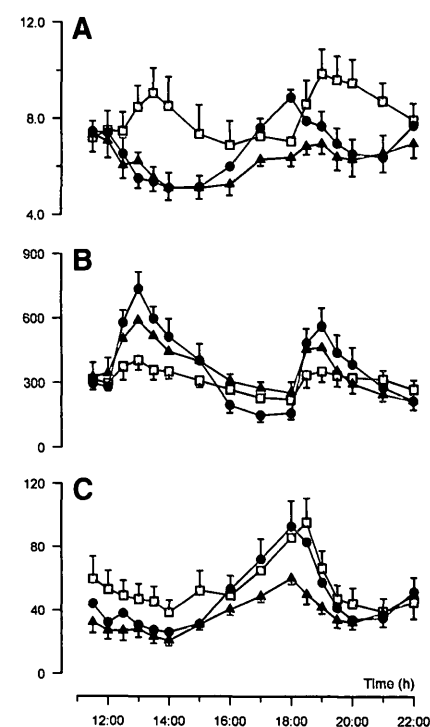
RESULTS

Blood glucose concentrations

Baseline. Baseline blood glucose concentrations before lunch at 1200 were compa-

rable on the 4 study days (Table 3, Fig. 1) **Early postlunch (1230–1500).** After lunch, mean blood glucose concentration on the standard human regular insulin treatment rose to a peak of 9.1 ± 1.1 mmol/l at 2 h after the insulin injection, while blood glucose concentrations fell on usual-dose lispro alone and on reduced-dose lispro plus NPH (Fig. 1). The average postprandial blood glucose concentration (1230–1500) was significantly lower after usual-dose lispro alone or reduced-dose lispro plus NPH compared with human regular insulin (5.5 ± 0.2 or 5.6 ± 0.2 vs. 8.2 ± 0.5 mmol/l, $P < 0.05$ for both), with no difference between the lispro regimens (Table 3, Fig. 1).

In the early postprandial period (1230–1500), blood glucose fell to hypoglycemic levels (blood glucose <3.0 mmol/l) in two patients on human regular insulin, four patients on usual-dose lispro alone, and three patients on the reduced-dose lispro plus NPH (NS).

Late postprandial (1500–1800). With the usual-dose lispro alone, blood glucose levels rose steadily from 1500 to 1800, whereas after human regular insulin, blood glucose levels declined from 2 h after the meal to a plateau from 1600 to 1800 (Fig. 1). In contrast, after reduced-dose lispro plus NPH, blood glucose levels increased insignificantly from 1500 until 1800. Accordingly, the pre-dinner (1800) blood glucose concentration was significantly higher after lispro alone than after either human regular insulin or reduced-dose lispro plus NPH (8.9 ± 0.3 vs. 7.1 ± 0.8 or 6.4 ± 0.4 mmol/l, $P < 0.05$ for both); the apparent difference between human regular insulin and reduced-dose lispro plus NPH did not reach statistical significance.

In the late postprandial period (1530–1800), blood glucose fell to hypoglycemic levels in three patients on human regular insulin, one patient on the reduced-

dose lispro plus NPH, and no patient on usual-dose lispro alone (NS).

Postdinner (1830–2200). With usual-dose lispro alone, blood glucose concentrations fell rapidly in the first hour, whereas those with human regular insulin rose (Fig. 1). Accordingly, despite the higher glucose levels at 1800, average postprandial glucose concentration (1830–2100) was significantly lower after lispro alone (7.1 ± 0.6 vs. 9.2 ± 0.9 mmol/l, $P < 0.005$). On reduced-dose lispro plus NPH, the lower blood glucose levels at 1800 remained essentially unchanged in the 3 h after dinner, giving average concentrations that are not different from usual-dose lispro alone (6.6 ± 0.5 vs. 7.1 ± 0.6 mmol/l) but are lower than with human regular insulin ($P < 0.005$).

Bedtime blood glucose concentrations (2200) were not different on the three insulin regimens (Table 3, Fig. 1).

In the postprandial period (postdinner: 1830–2200), blood glucose fell to hypoglycemic levels in one patient on human regu-
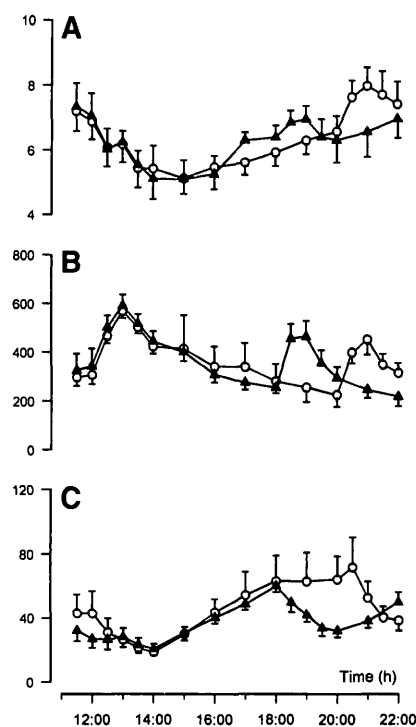
Figure 2—*Daytime blood glucose (mmol/l) (A), plasma free insulin (pmol/l) (B), and blood 3-hydroxybutyrate (μmol/l) (C) concentrations (means ± SEM) in type 1 diabetic patients after subcutaneous injection of premeal lispro in a reduced dose plus supplemental NPH insulin dose, with the evening meal given at the usual time (1800) (▲) or delayed by 2 h to 2000 (O).*

Table 4—*Plasma free insulin concentrations (pmol/l)*

	Standard insulin	Usual lispro alone	Lispro + NPH
Baseline (1200)	298 ± 48	282 ± 19	307 ± 37
Postprandial (1230–1500)	360 ± 49	556 ± 64*	491 ± 34*
Peak insulin concentration	404 ± 62	737 ± 128*	590 ± 13*
Preprandial (1800)	223 ± 30†	159 ± 29*	254 ± 22†
Postprandial (1830–2100)	332 ± 25	430 ± 35*	462 ± 35*
Pre-bedtime (2200)	269 ± 42	216 ± 48	217 ± 40

Data are means ± SEM. *$P < 0.05$ compared with standard human regular insulin; †$P < 0.001$ compared with usual-dose lispro alone.

lar insulin, two patients on lispro alone, and one patient on the reduced-dose lispro plus NPH (NS).

Delayed evening meal study. Blood glucose concentrations were very similar up to 1800 on the 2 study days when reduced-dose lispro plus NPH was given at lunchtime (Fig. 2). Between 1800 and 2000 on the study day when the evening meal was given 2 h later, blood glucose concentrations did not change significantly, being 6.4 ± 0.4 mmol/l at 1800, and 6.5 ± 0.4 mmol/l at 2000 (Fig. 2).

Plasma free insulin

Baseline plasma free insulin concentrations before lunch at 1200 were comparable on all study days (Table 4 and Fig. 1).

After subcutaneous injection of insulin lispro, whether usual-dose lispro alone or reduced-dose lispro plus NPH, insulin concentration rose rapidly, reaching a higher and earlier peak within 1 h of insulin injection (Fig. 1). In contrast, after subcutaneous injection of the premeal unmodified human insulin, plasma insulin concentration rose slowly to a broad plateau, peaking

2 h after insulin injection (Fig. 1). As a result, the peak insulin concentration was significantly higher after either of the lispro treatments, usual-dose or reduced-dose, compared with unmodified human insulin treatment (Table 4). Although the peak insulin concentration was apparently higher with usual-dose lispro compared with reduced-dose lispro, the difference was not statistically significant.

The average early postprandial plasma insulin concentration—whether postlunch (1230–1500) or postdinner (1830–2100)—was significantly lower after unmodified human insulin compared with either usual-dose lispro alone or reduced-dose lispro plus NPH (Table 4, Fig. 1). However, there was no difference in the average early postprandial insulin concentration between the two lispro regimens, the usual-dose or the reduced-dose, after lunch.

Plasma insulin concentrations after usual-dose lispro alone continued to decline rapidly from 1330, reaching a level lower than that after the other treatments at 1600, and continued at that level until the time of the pre-evening meal insulin dose at 1800 (Fig. 1). As a result, the late postprandial (at 1800) insulin concentration was lower after usual-dose lispro alone compared with either unmodified human insulin or reduced-dose lispro plus NPH insulin (159 ± 29 vs. 223 ± 30 or 254 ± 22 pmol/l, $P < 0.05$ for both) (Table 4). In contrast, after reduced-dose lispro plus NPH, insulin concentration declined slowly and insignificantly from 1300 until 1600; then insulin levels were maintained from 1600 until 1800, the time of pre-evening meal insulin dose at a level not different from that after unmodified human insulin and similar to the baseline level (Fig. 1).

Delayed evening meal study. Plasma insulin profiles were similar up to 1800 on the 2 study days when reduced-dose lispro plus supplemental NPH insulin was given

at lunchtime (Fig. 2). Between 1800 and 2000 on the study day when the pre-evening meal lispro was given 2 h later, plasma insulin concentration did not change significantly during the 2-h delay, being 281 ± 59 pmol/l at 1800 and 241 ± 49 pmol/l at 2000.

Blood intermediary metabolites

Blood 3-hydroxybutyrate levels were suppressed from lunchtime at 1230 until 1500 (Fig. 1) in all study days. With the lispro alone, 3-hydroxybutyrate levels rose steadily from 1500 to a peak at 1800, and the levels were suppressed again from dinnertime. With human regular insulin, the 3-hydroxybutyrate profile was similar to the profile with the lispro alone. In contrast, with the reduced-dose lispro plus NPH, 3-hydroxybutyrate levels remained largely unchanged throughout the study day, with a peak of 60 ± 4 μmol/l at 1800. Although with the reduced-dose lispro plus NPH, the preprandial 3-hydroxybutyrate at 1800 was lower than that with either lispro alone or human regular insulin (60 ± 4 vs. 93 ± 17 or 87 ± 14 μmol/l, $P > 0.05$ for both) (Fig. 1), the difference was clinically insignificant and the 3-hydroxybutyrate levels were within physiological limits at all times (Fig. 1).

Blood glycerol levels echoed the profiles of 3-hydroxybutyrate on all study days (data not shown).

Blood lactate, pyruvate, and alanine concentrations and profiles did not differ between human regular insulin, usual-dose lispro alone, and reduced-dose lispro plus NPH (data not shown).

On the delayed evening meal study day, during the 2 h between the usual mealtime and the delayed mealtime, 3-hydroxybutyrate levels remained unchanged (63 ± 16 μmol/l at 1800; 64 ± 14 μmol/l at 2000) (Fig. 2). Blood glycerol levels echoed the 3-hydroxybutyrate profile on both the

delayed and usual evening meal study day with reduced-dose lispro plus NPH (data not shown).

CONCLUSIONS — The main objective of the present study was to assess the metabolic efficacy of optimization of the daytime basal insulin requirement in patients with a 6-h or longer interprandial interval when using the short-acting insulin analog lispro. This was done by comparing the daytime blood glucose control achieved by patients receiving either premeal lispro alone or premeal lispro plus supplemental NPH, compared with standard human regular insulin, with total insulin dose unchanged. Only C-peptide–negative type 1 diabetic patients with preceding fairly good metabolic control participated in the study, in order to avoid large interindividual differences in insulin sensitivity. An open-label design was necessary to make it possible to vary the dose of premeal lispro and to give NPH insulin on two of the study days. A crossover design, limits on blood glucose concentrations at baseline, and strict standardization of meal content and timing all serve to maintain statistical power in a small and intensive study.

The present study confirmed that lispro is advantageous, compared with human regular insulin, for controlling early postprandial glycemia, as reported previously (14–22). The improvement in postprandial glucose control with insulin lispro was evident after both lunch and dinner. More importantly, the significant improvement in postprandial blood glucose control was also achieved with a reduced dose of lispro (with NPH), and indeed immediate postprandial glycemia was identical compared with a usual dose of lispro injected before a similar meal (Fig. 1). The reduction of lispro dose (30%) was chosen on the basis that postprandial glucose control would remain improved given that *1*) previous studies at unchanged dose resulted in considerable biochemical hypoglycemia (12,17) with likely counterregulatory hormone effects; *2*) other clinical laboratory studies have suggested that unchanged lispro dose preprandially may be too high (12,33); and *3*) a reduced evening premeal lispro dose gave equivalent blood glucose control after dinner in a study of optimal nighttime insulin dosage (34).

This study design might tend to render favorable results for insulin lispro, because the differences in postprandial blood glucose excursions between lispro and human

regular insulin would have been smaller if human regular insulin had been injected 30 min before the meal. From the pharmacokinetic point of view, there may be an advantage for an injection–meal interval (35–37) because of the slow absorption of human regular insulin after subcutaneous injection (6–8). However, such an interval is known to be inconvenient to patients—the majority of whom do not follow it—and may be dangerous unless glucose levels have been measured (26–29). The present study was therefore performed under conditions closer to normal patient practice.

The basal insulin delivery between the main meals and in the early part of the night in the regimen of premeal human regular plus basal insulin is supplied by the protracted absorption of the premeal short-acting human regular insulin, which may last for up to 8 h. In contrast, the duration of action of lispro proved too short to maintain blood glucose control for even 6 h in the present study. This deterioration of the glycemic and metabolic control between meals may be one of the main reasons for the difficulties in demonstrating an improvement in the overall blood glucose control with insulin lispro (18–22), in particular in patients using the premeal plus basal insulin regimens.

However, the present study has also clearly demonstrated that an appropriate dose of NPH can be chosen to prevent the preprandial deterioration of glucose levels noted with the lispro regimen (21–24). We chose a dose based on the 30% reduction in lispro dose at both the current (lunch) and the next (dinner) meal, thus keeping the total insulin dose equivalent for experimental purposes and resulting in an approximate 50:50 mixture of lispro:NPH at lunchtime. The supplemental dose of NPH proved able to prevent any such hyperglycemia between the meals; indeed, if anything, blood glucose levels were lower 4–6 h after lunch on lispro plus NPH compared with human regular insulin.

In using fixed doses of lispro and NPH (15) or of human ultratard insulin rather than NPH insulin (16), prolongation of control of late postprandial glucose levels for up to 8 h has been demonstrated. Flexibility of meal timing is an important advantage of multiple insulin injections regimens, and it is possible with human regular insulin without adverse impact on blood glucose control (25). The current results show that when NPH insulin dose is chosen on the basis of current human regular insulin

mealtime doses, blood glucose control can be maintained up to at least 8 h after the last injection of lispro plus NPH insulin.

Although hypoglycemia was not a problem with the optimized basal insulin regimen in the present study, the study could not have the power to address that question adequately.

To prevent the deterioration of blood glucose control in the early part of the night (17), with an insulin analog regimen, the evening basal insulin requirement should be adequately replaced. This can be achieved with optimization of the evening basal extended-acting insulin dose (37). Thus, we might conclude that optimization of both day and night basal insulin requirement can now be achieved in short-acting insulin analog regimens, perhaps allowing demonstration of an overall improvement in blood glucose control as has been shown for lispro in a continuous subcutaneous insulin infusion regimen (38). However, it remains to be confirmed whether such optimization of the basal insulin requirement will mask the most desirable advantage of short-acting insulin analogs, namely the reduction in the incidence of hypoglycemia (17–19), in particular nighttime hypoglycemia (17).

The present study has clearly demonstrated that the combination of lunchtime lispro and NPH insulin maintained the improvement in late as well as early postprandial blood glucose control, with no daytime deterioration in glycemic control from lunchtime to the bedtime at 2200. However, the results of the present study are limited to daytime blood glucose control and did not assess nighttime hypoglycemia with the optimal daytime NPH insulin dose with insulin lispro; even the daytime was limited to the period between lunch and bedtime, leaving the daytime period between breakfast and lunch not tested on the optimal daytime regimen.

In conclusion, the present study has demonstrated that the short-acting insulin lispro results in improved postprandial blood glucose control, even when given at 70% of the usual premeal dose, compared with human regular insulin. However, because of its short duration of action, insulin lispro is unable to prevent a deterioration in late postprandial blood glucose control after 5–6 h. Our data, however, suggest that insulin lispro plus supplemental NPH is an effective regimen for improving early and late postprandial glycemic control for up to 8 h.

References

1. DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med* 329:977–985, 1993

2. Wang PH, Lau J, Chalmers TC: Meta-analysis of effects of intensive blood-glucose control on late complications on type 1 diabetes. *Lancet* 341:1306–1309, 1993

3. Zinman B: Insulin regimen and strategies for IDDM. *Diabetes Care* 16 (Suppl. 3):24–28, 1993

4. Home PD, Thow JC, Tunbridge FKE: Insulin treatment: a decade of change. *Br Med Bull* 45:92–110, 1989

5. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR: [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analog of human regular insulin. *Diabetes* 43:396–402, 1994

6. Berger M, Cuppers HJ, Hegner H, Jörgens V, Berchtold P: Absorption kinetics and biologic effects of subcutaneous injected insulin preparations. *Diabetes Care* 5:77–91, 1982

7. Gardner DF, Arakaki RF, Podet EJ, Nell LJ, Thomas JW, Field JB: The pharmacokinetics of subcutaneous regular insulin in type 1 diabetic patients: assessment using glucose clamp technique. *J Clin Endocrinol Metab* 63:689–694, 1986

8. Home PD, Pickup JC, Keen H, Alberti KGMM, Parson JA, Binder C: Continuous subcutaneous insulin infusion: comparison of plasma insulin profile after infusion or bolus injection of meal-time dose. *Metabolism* 30:439–442, 1981

9. Brange J, Ribel U, Hansen JF, Dodson G, Hansen MT, Havelund S, Melberg SG, Norris F, Norris K, Snel L, Sorensen AR, Voigt HO: Monomeric insulin obtained by protein engineering and their medical implications. *Nature* 333:679–682, 1988

10. Brange J, Owen DR, Kang S, Volund A: Monomeric insulin and their experimental and clinical implications. *Diabetes Care* 13:923–954, 1990

11. Heinemann L, Starke AAR, Heding L, Jensen I, Berger M: Action profiles of fast onset insulin analogues. *Diabetologia* 33:384–386, 1990

12. Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vincenzo A, Epifano L, Ciofetta M, Pampabelli S, Brunetti P, Bolli GN: Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28), Pro(B29)] in IDDM. *Diabetologia* 37:713–720, 1994

13. ter Braak EW, Bianchi R, Erkelens DW: Faster, shorter and more profound action of [Lys(B28), Pro(B29)] human regular insulin analogue compared to regular insulin irrespective of the injection site (Abstract). *Diabetes* 42 (Suppl. 1):207A, 1993

14. Heinemann L, Heise T, Wahl L Ch, Trautmann ME, Starke AAR: Prandial glycaemia after a carbohydrate-rich meal in type 1 diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro(P29)] human regular insulin. *Diabet Med* 13:625–629, 1996

15. Burge MR, Waters DL, Holcombe JH: Prolonged efficacy of short-acting insulin lispro in combination with human Ultratard in insulin dependent diabetes mellitus. *J Clin Endocrinol Metab* 82:920–924, 1997

16. Torlone E, Modarelli F, Pampanelli S, Epifano L, Lalli C, Kassi G, Del Sindaco P, Perriello G, Di Vincenzo A, Brunetti P, Rambotti AM, Bolli G: Effects of the short-acting insulin analog [Lys(B28),Pro(B29)] on postprandial blood glucose control in IDDM. *Diabetes Care* 19:945–952, 1996

17. Ahmed ABE, Home PD: The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. *Diabetes Care* 21:32–37, 1998

18. Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK: Pre-meal insulin analogue lispro vs. Humulin R insulin treatment in young subjects with type 1 diabetes. *Diabet Med* 13:47–52, 1996

19. Anderson JH Jr, Brunelle RL, Koivisto VA, Pfützner A, Trautmann ME: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 46:265–270, 1997

20. Pfützner A, Kustner E, Forst T, Schulze-Schleppinghoff B, Trautmann ME, Haslbeck M, Schatz H, Beyer J: Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol* 104:25–30, 1996

21. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH: Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care* 20:1827–1832, 1997

22. Jacobs MAJM, Keulen ETP, Kanc K, Casteleijn S, Scheffer P, Deville W, Heine RJ: Metabolic efficacy of preprandial administration of Lys(B28),Pro(29) human insulin analog in IDDM patients. *Diabetes Care* 20:1279–1286, 1997

23. Rowe R, Anderson JH, Gale E: A double-blind comparison of insulin lispro and regular insulin in patients on a multiple injection regimen (Abstract). *Diabetes* 45 (Suppl. 1):A71, 1996

24. Nielsen FS, Jörgensen LN, Ipsen M, Voldsgaard AI, Parving HH: Long-term comparison of human regular insulin analogue B10Asp and soluble human regular insulin in IDDM patients on a basal/bolus insulin regimen. *Diabetologia* 38:592–598, 1995

25. Tunbridge FKE, Home PD, Murphy M, Alberti KGMM: Does flexibility at mealtime disturb glucose control on a multiple insulin injection regimen? *Diabet Med* 8:833–838, 1991

26. Jörgensen LN, Nielsen FS: Timing of premeal insulins in diabetic patients on a multiple daily injection regimen: a questionnaire study (Abstract). *Diabetologia* 33 (Suppl. 1):A116, 1990

27. Berger M, Heinemann L: Are presently available insulin analogues clinically beneficial? (Letter) *Diabet Med* 40 (Suppl. 2):S91–S96, 1997

28. Heinemann L: Do insulin treated diabetic patients use an injection-meal interval in daily life? (Letter). *Diabet Med* 12:449–450, 1995

29. Heinemann L, Starke AAR, Hohmann A, Berger M: Timing between the subcutaneous administration of insulin and consumption of a carbohydrate rich meal. *Horm Metab Res* 10 (Suppl. 26):137–139, 1992

30. Hanning I, Home PD, Alberti KGMM: Measurement of free insulin concentration: the influence of the timing of extraction of insulin antibodies. *Diabetologia* 28:831–835, 1985

31. Soeldner JS, Slone D: Critical variables in the RIA of serum insulin using the double antibody technic. *Diabetes* 14:771–779, 1965

32. Harrison J, Hodson AW, Skillen AW, Stappenbeck R, Agius L, Alberti KGMM: Blood glucose, lactate, pyruvate, glycerol, 3-hydroxybutyrate, and acetoacetate measurements in man using a centrifugal analyser with fluorimetric attachment. *J Chem Clin Biochem* 26:141–146, 1988

33. Burge MR, Castillo KR, Schade DS: Meal composition is a determinant of lispro-induced hypoglycemia in IDDM. *Diabetes Care* 20:152–155, 1997

34. Ahmed ABE, Mallias J, Home PD: Optimization of evening insulin dose in patients using the short-acting insulin analog lispro. *Diabetes Care* 21:1162–1166, 1998

35. Patrick AW, Collier A, Matthews DM, Macintyre CCA, Clarke BF: The importance of the time interval between insulin injection and breakfast in determining postprandial glycaemic control: a comparison between human and porcine insulin. *Diabet Med* 5:32–35, 1988

36. Dimitriadis G, Gerich J: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 6:374–377,

1985

37. Lean MEJ, Ng LL, Tennison BR: Interval between insulin injection and eating in rela-tion to blood glucose control in adult dia-betics. *Br Med J* 290:105–108, 1985

38. Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T: Insulin lispro in CSII: results of a double blind study. *Diabetes* 46:440–443, 1997