The Effect of the Insulin Analog Lispro on Nighttime Blood Glucose Control in Type 1 Diabetic Patients

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

OBJECTIVE — Unmodified regular insulin has a long absorption tail, unlike the fast-acting insulin analog lispro, and may contribute to hypoglycemia in the early part of the night. A randomized crossover double-blind study was performed to compare blood glucose concentrations in the early part of the night in type 1 diabetic patients receiving lispro or unmodified regular human insulin, in random order, on 2 separate study days.

RESEARCH DESIGN AND METHODS — We studied 23 C-peptide–negative patients; 12 were using a premeal plus basal insulin regimen, and 11 were using twice-daily insulin injections. Patients were admitted to the investigation unit at 5:00 P.M. and received a single dose of lispro or unmodified regular human insulin before the evening meal. In both groups, the NPH insulin dose remained unchanged. Identical meals and snacks were eaten at the same time during both study days.

RESULTS — Average postprandial (6:00–10:00 P.M.) blood glucose concentrations were significantly lower after lispro therapy compared with human insulin (7.1 ± 0.4 [SE] vs. 8.5 ± 0.4 mmol/l, $P = 0.0002$). Nighttime (midnight to 4:00 A.M.) blood glucose concentrations were significantly higher after lispro compared with human insulin (10.3 ± 0.4 vs. 9.1 ± 0.4 mmol/l, $P = 0.02$). This difference was greatest in patients on the premeal plus basal insulin regimen (11.6 ± 0.5 vs. 8.7 ± 0.4 mmol/l, $P < 0.001$). The incidence of nocturnal hypoglycemia (midnight to 4:00 A.M., blood glucose <3.5 mmol/l) was less with lispro compared with unmodified insulin (1 vs. 6 patients, $P = 0.04$). Nighttime (midnight to 4:00 A.M.) 3-hydroxybutyrate (102 ± 13 vs. 51 ± 7 μmol/l, $P = 0.000$) and glycerol (52 ± 3 vs. 42 ± 2 μmol/l, $P < 0.01$) were significantly higher after lispro therapy compared with human insulin in patients on the premeal plus bolus insulin regimen.

CONCLUSIONS — Lispro can improve postprandial blood glucose control and reduce the incidence of nocturnal hypoglycemia at the expense of nocturnal hyperglycemia and hyperketonemia in patients using a premeal plus basal insulin regimen.

In clinical practice, it is generally assumed that hypoglycemia in the early part of the night (midnight to 3:00 A.M.) is due to high plasma insulin concentrations at that time as a consequence of the profile of absorption of extended-acting insulin preparations (1–3). However, it is well recognized that, while the onset of action of unmodified (regular, soluble) insulin may be as soon as 30 min after injection, a significant glucose-lowering effect may extend to 6–8 h after insulin injection (4–10). Accordingly, blood glucose concentration after injection of unmodified (regular) insulin at any time after 6:00 P.M. may be lowered at any time up to 2:00 A.M. or later if absorption of food is no longer occurring. The combined effect with the early phase of absorption of the nighttime extended-acting insulin is likely to be particularly significant.

The fast-acting human insulin analog lispro is absorbed more quickly and has a faster onset and shorter duration of action than unmodified regular human insulin (11–17). Accordingly, patients using lispro before their evening meal might be expected to have higher blood glucose levels and, thus, less risk of hypoglycemia in the early part of the night. This hypothesis has therefore been tested in people with type 1 diabetes using either a premeal plus basal insulin regimen or twice-daily insulin injections.

RESEARCH DESIGN AND METHODS

— This was a randomized crossover double-blind comparative study conducted in two groups of patients attending a specialist diabetes service.

Patients

Twenty-three 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.

Twelve patients were using a premeal plus basal insulin regimen, and 11 were using twice-daily insulin injections. In all cases, the extended-acting insulin used was NPH. All patients had been stable on insulin for more than 1 year, with HbA_{1c} of 7.8 ± 0.9% (mean ± 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. Patients' clinical characteristics are given in Table 1. All patients were healthy, apart from their diabetes, and did not have late diabetic complications.

Methods

Each patient was studied on 2 separate days, at a 1- to 4-week interval. At 1–3 weeks before the first study day, patients were screened by medical history, physical examination, blood count, and serum biochemical analysis.

On each study day, 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 5:00 P.M. for overnight

From the Human Metabolism and Diabetes Research Centre, University of Newcastle upon Tyne, Newcastle upon Tyne, U.K.

Address correspondence and reprint requests to Philip D. Home, DM, DPhil, FRCP, Human Metabolism and Diabetes Research Centre, University of Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, U.K. E-mail: philip.home@ncl.ac.uk.

Received for publication 4 June 1997 and accepted in revised form 8 September 1997.

study. 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 5:00 P.M., or whose blood glucose concentrations were more than 2.5 mmol/l different on study day 2 from study day 1, were requested to return another day.

Patients had an evening meal from a choice of foods at 6:00 P.M. The choice of foods and amount were recorded, and an identical meal and snacks were given at the same time on study day 2. At 5 min before the evening meal, in a double-blind manner according to a randomization schedule, patients received a subcutaneous injection of either the insulin analog lispro (Humalog, Lilly, Basingstoke, U.K.) or unmodified human insulin (Humulin S, Lilly) into the abdominal wall of the periumbilical region by means of a pen injector. The dose of lispro or human insulin administered before the evening meal on each of the study days was each patient's usual insulin dose at that time and was the same dose on both study days (premeal plus basal regimen: 10 ± 3 (mean ± SD) U; twice-daily regimen: 10 ± 5 U). Patients on a premeal plus basal insulin regimen received their injection of extended-acting insulin at 10:00 P.M., and patients on the twice-daily insulin regimen received their extended-acting insulin at same time as they received their short-acting insulin by separate injection. The dose and type of extended-acting insulin were unchanged from the patient's usual regimen (premeal plus basal regimen: 17 ± 5 U; twice-daily regimen: 13 ± 6 U).

Blood samples for measurement of blood glucose, plasma free insulin, serum growth hormone, and blood intermediary metabolite concentrations were obtained at 5:30 P.M., 6:00 P.M., and then hourly until 8:00 A.M.

If blood glucose concentrations fell to <3.5 mmol/l, blood sampling frequency was increased to half-hourly. Patients were treated only if they were symptomatic or developed restlessness plus biochemical hypoglycemia during sleep. Symptomatic hypoglycemia or restlessness plus hypoglycemia during sleep were managed with a 20-g carbohydrate snack, which was repeated if symptoms did not abate within 10 min. Treatment of hypoglycemia before midnight on either study day was taken as invalidating that study day, and the patient was invited to repeat the study day at a later date. Treatment of hypoglycemia from midnight to 8:00 A.M. was taken as invalidating metabolic data collected after the time of that treatment.

A blood glucose of <3.5 mmol/l in the absence of symptoms before midnight and with or without symptoms between midnight and 4:00 A.M. was taken as the endpoint for analysis and comparison of the incidence of hypoglycemia.

Biochemical analysis

Blood glucose was measured using a glucose oxidase method (Yellow Springs Instruments Model 2300 Stat Plus Glucose Analyzer, Yellow Springs, OH). Glucose was measured in whole blood within 2 min of blood samplings.

To remove antibody-bound insulin, plasma was mixed with an equal volume of 30% polyethylene glycol immediately after blood collection (18). Plasma free insulin was measured by radioimmunoassay (19), using insulin or lispro standards as appropriate. Serum C-peptide was measured by an enzyme-linked immunosorbent assay using a commercially available kit (Dako Insulin, Ely, U.K.). Blood intermediary metabolites were measured as previously described (20). Plasma growth hormone was measured using immunoradiometric assay reagents (Netria, London, U.K.)

Statistical analysis

The primary hypothesis was set for mean blood glucose concentrations in the early part of the night (midnight to 4:00 A.M.), with secondary hypotheses for biochemical hypoglycemia in this and other time periods and blood glucose concentrations in other time periods.

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 ± SE unless stated otherwise. Statistical comparison was by paired Student's *t* test. Logarithmic transformation was used to correct skewed distributions.

The blood glucose level for biochemical hypoglycemia was set at <3.5 mmol/l. Biochemical hypoglycemic episodes with blood glucose <3.5 mmol/l in the absence of symptoms before midnight and with or without symptoms between midnight and 4:00 A.M. were taken as the endpoint for analysis and comparison.

The occurrence of hypoglycemia in those on lispro and in those on unmodified human insulin was compared using Fisher's exact test. Other observations are reported as a matter of observation only.

Table 1—*Clinical characteristics of the patients studied*

Patients (*n*)	23
Premeal basal regimen (*n*)	12
Twice-daily regimen (*n*)	11
Sex (M/W)	10/13
Age (years)	36 ± 11
BMI (kg/m²)	25.3 ± 3.4
Duration of diabetes (years)	13 ± 10
Daily insulin dose (U)	43 ± 10
HbA_{1c} (%)	7.8 ± 0.9
Serum C-peptide (nmol/l)	0.10 ± 0.05

Data are means ± SD or *n*. Normal HbA_{1c} <6.1%.

RESULTS

Blood glucose concentrations

Evening. Baseline blood glucose concentrations before the evening meal at 6:00 P.M. were comparable on the 2 study days (insulin vs. lispro: 6.5 ± 0.5 vs. 6.6 ± 0.5 mmol/l) (Table 2).

Average postprandial blood glucose concentrations (6:00–10:00 P.M.) were significantly lower after lispro compared with unmodified insulin (7.1 ± 0.4 vs. 8.5 ± 0.4 mmol/l, $P < 0.001$), a difference mainly due to the patients on the premeal plus basal insulin regimen (6.2 ± 0.4 vs. 8.2 ± 0.4 mmol/l, $P < 0.001$). Inspection of the blood glucose profiles (Fig. 1) shows a more rapid fall in postprandial glucose concentrations with lispro, converging again by 10:00 P.M. Maximum difference in postprandial blood glucose concentrations between lispro and human insulin was found 2 h after the meal (at 8:00 P.M.) and was 4.4 ± 1.0 mmol/l on the premeal plus bolus regimen ($P < 0.01$) and 1.3 ± 1.1 mmol/l on the twice-daily insulin regimen ($P > 0.05$). Of patients on the premeal plus basal insulin regimen, the average blood glucose concentration 2 h after insulin injection (at 8:00 P.M.) was 4.8 ± 0.8 mmol/l with 95% CI 3.1–6.4 mmol/l after lispro therapy compared with 9.1 ± 1.1 mmol/l with 95% CI 6.1–11.6 mmol/l after unmodified human insulin therapy ($P = 0.0015$).

Blood glucose fell to hypoglycemic levels in six patients on lispro and two patients on unmodified insulin ($0.10 > P > 0.05$).

Nighttime. Average nighttime blood glucose concentration (midnight to 4:00 A.M.) on the premeal plus basal regimen was

Table 2—*Blood glucose concentrations after subcutaneous lispro or unmodified human insulin injection*

Time	Insulin regimen	Blood glucose concentrations (mmol/l) Lispro	Insulin	P
Baseline (6:00 P.M.)	Premeal plus basal	6.4 ± 0.6	6.6 ± 0.7	NS
	Twice daily	6.5 ± 0.7	6.4 ± 0.7	NS
	All patients	6.6 ± 0.5	6.5 ± 0.5	NS
Postprandial (6:00–10:00 P.M.)	Premeal plus basal	6.2 ± 0.4	8.2 ± 0.4	0.0002
	Twice daily	8.0 ± 0.5	8.3 ± 0.6	NS
	All patients	7.1 ± 0.4	8.5 ± 0.4	0.0002
Prebed (10:00 P.M.)		8.5 ± 0.9	8.4 ± 1.2	NS
	Twice daily	9.6 ± 1.1	9.5 ± 1.7	NS
	All patients	8.8 ± 0.7	9.1 ± 1.0	NS
Nighttime (midnight to 4:00 A.M.)	Premeal plus basal	11.6 ± 0.5	8.7 ± 0.4	0.000
	Twice daily	8.7 ± 0.6	9.8 ± 0.7	NS
	All patients	8.8 ± 0.7	9.1 ± 0.4	0.02
Fasting (8:00 A.M.)	Premeal plus basal	12.4 ± 1.0	9.7 ± 1.3	0.037
	Twice daily	10.5 ± 1.5	11.8 ± 1.6	NS
	All patients	11.3 ± 1.0	10.4 ± 1.3	NS

Data are means ± SE.

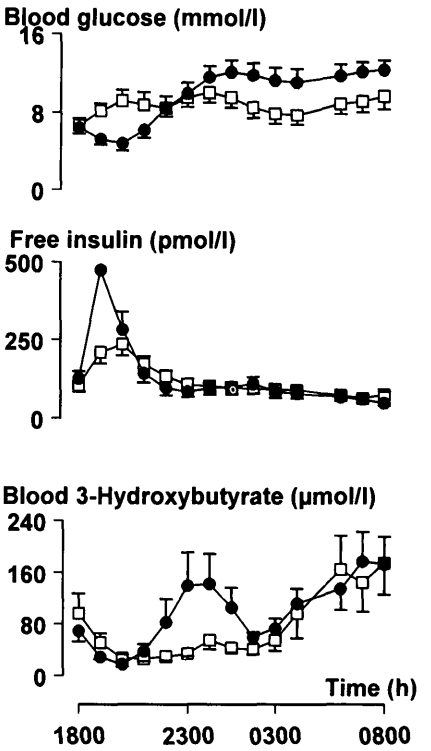

Figure 1—*Evening and nighttime (6:00 P.M. to 8:00 A.M.) blood glucose, plasma free insulin, and blood 3-hydroxybutyrate concentrations (means ± SE) in patients using the premeal plus basal insulin regimen after subcutaneous injection of unmodified human insulin (□) lispro (●).*

significantly higher after lispro therapy compared with unmodified insulin (11.6 ± 0.5 vs. 8.7 ± 0.4 mmol/l, $P < 0.001$). However, no significant difference in early nighttime glucose concentrations was found on the twice-daily insulin regimens (8.4 ± 0.6 vs. 9.5 ± 0.7 mmol/l) (Table 2).

Inspection of the blood glucose profile shows that glucose concentrations rose steadily on the premeal plus basal insulin regimen on the lispro study day from 9:00 P.M. onward and that the difference persisted for the most part throughout the night. The maximum difference was found at 3:00 A.M. and was 3.4 ± 1.3 mmol/l ($P < 0.05$).

Blood glucose concentrations fell to hypoglycemic levels in one patient on lispro and six patients on unmodified insulin ($P < 0.05$) between midnight and 4:00 A.M. Nighttime hypoglycemia (midnight to 4:00 A.M.) included all biochemical hypoglycemic episodes, whether symptomatic or asymptomatic and treated or untreated.

Fasting. Fasting blood glucose concentrations (8:00 A.M.) appeared higher after lispro therapy compared with human insulin in patients on the premeal plus basal regimen (12.4 ± 1.0 vs. 9.7 ± 1.3 mmol/l) ($P = 0.037$) (Table 2).

There was no difference in fasting blood glucose concentration between lispro and human insulin in patients using the twice-daily insulin regimen (10.2 ± 1.5 vs. 11.2 ± 1.6 mmol/l) (Table 2).

Plasma free insulin

Baseline plasma free insulin concentrations before the evening meal at 6:00 P.M. were comparable on both study days (insulin vs. lispro: 123 ± 20 vs. 148 ± 23 pmol/l) (Table 3).

After lispro injection, plasma insulin concentrations peaked earlier and declined faster than after human insulin (Figs. 1 and 2). Maximum postprandial insulin concentration was significantly higher after lispro than after unmodified insulin (475 ± 65 vs. 257 ± 35 pmol/l, $P < 0.001$) for patients using the premeal plus basal regimen and for all patients (413 ± 42 vs. 295 ± 29 pmol/l, $P < 0.05$). Maximum insulin concentration was reached earlier after the lispro injection (Figs. 1 and 2).

In patients on the premeal plus basal regimen, average postprandial (6:00–10:00 P.M.) insulin concentrations were significantly higher for lispro compared with human insulin (224 ± 26 vs. 180 ± 14

Table 3—*Free insulin concentrations after lispro or unmodified insulin injection*

Time	Insulin regimen	Free insulin concentrations (pmol/l) Lispro	Insulin	P
Baseline (6:00 P.M.)	Premeal plus basal	139 ± 22	113 ± 20	NS
	Twice daily	171 ± 25	170 ± 31	NS
	All patients	148 ± 23	123 ± 20	NS
Postprandial (6:00–10:00 P.M.)	Premeal plus basal	224 ± 26	180 ± 14	0.014
	Twice daily	228 ± 19	215 ± 18	NS
	All patients	226 ± 16	197 ± 11	0.030
Nighttime (midnight to 4:00 A.M.)	Premeal plus basal	95 ± 10	98 ± 6	NS
	Twice daily	118 ± 10	105 ± 8	NS
	All patients	106 ± 7	101 ± 5	NS

Data are means ± SE.

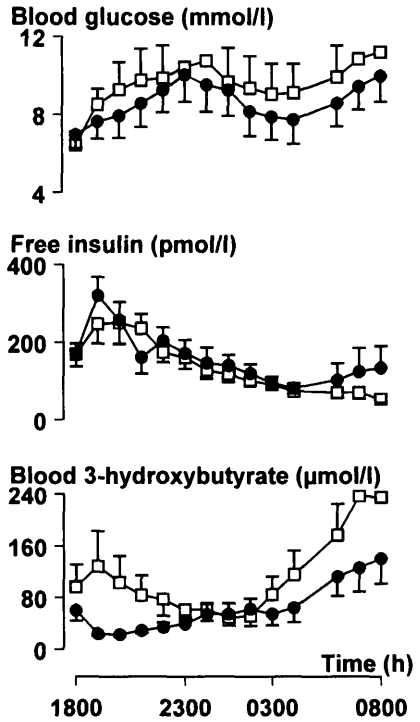

Figure 2—*Evening and nighttime (6:00 P.M. to 8:00 A.M.) blood glucose, plasma free insulin, and blood 3-hydroxybutyrate concentrations (means ± SE) in patients using the twice-daily insulin regimen after subcutaneous injection of unmodified human insulin (□) or lispro (●).*

pmol/l, $P = 0.014$) (Table 3). However, in patients on twice-daily insulin regimens, there is no significant difference (228 ± 19 vs. 215 ± 18 pmol/l) (Table 3, Fig. 2).

There was no difference found in the average nighttime (midnight to 4:00 A.M.) insulin concentrations on either regimen (Table 3).

Growth hormone concentrations

Baseline growth hormone concentrations at 6:00 P.M. were similar on both study days and in both study groups. No differences were found between lispro and unmodified insulin studies in either group in any time period. A typical nocturnal profile was found in both study groups (Table 4, Fig. 3).

Blood intermediary metabolites

Blood lactate, pyruvate, and alanine concentrations and profiles did not differ between lispro and insulin on either regimen (data not shown).

Blood 3-hydroxybutyrate and glycerol were also similar between lispro and insulin on the twice-daily insulin regimen (Fig. 2). However, on the premeal plus basal insulin regimen, 3-hydroxybutyrate rose steadily from 9:00 P.M. to a peak at 11:00 P.M. and remained elevated and significantly higher after lispro therapy compared with human insulin during the night (midnight to 4:00 A.M., 102 ± 13 vs. 51 ± 7 μmol/l, $P < 0.001$) (Fig. 1). In patients on the premeal plus basal insulin regimen, fasting 3-hydroxybutyrate concentrations (8:00 A.M.) after lispro therapy were not different from those after human insulin (173 ± 42 vs. 174 ± 48 μmol/l). In patients on the premeal plus basal insulin regimen, 3-hydroxybutyrate concentrations after lispro increased steadily throughout the night and the early morning, while those after human insulin increased only during the early hours of the morning, reaching a level similar to that after lispro at the end of the study (8:00 A.M.).

Blood glycerol levels echoed the profile of 3-hydroxybutyrate concentrations in patients on the premeal plus basal insulin regimen (midnight to 4:00 A.M., 52 ± 3 vs. 42 ± 2 μmol/l, $P < 0.01$).

Table 4—*Growth hormone concentrations after lispro or unmodified insulin injection*

Time	Insulin regimen	Growth hormone concentrations (μg/l) Lispro	Insulin	P
Baseline (6:00 P.M.)	Premeal	6.7 ± 2.3	7.1 ± 2.9	NS
	Twice daily	4.4 ± 1.6	5.0 ± 1.5	NS
	All patients	5.6 ± 1.4	5.5 ± 1.7	NS
Postprandial (6:00–10:00 P.M.)	Premeal	5.2 ± 1.1	3.6 ± 0.7	NS
	Twice daily	2.3 ± 0.5	2.1 ± 0.4	NS
	All patients	3.8 ± 0.6	2.9 ± 0.4	NS
Nighttime (midnight to 4:00 A.M.)	Premeal	5.6 ± 1	7.4 ± 1.2	NS
	Twice daily	9.2 ± 2.0	7.4 ± 1.4	NS
	All patients	7.2 ± 1.1	7.5 ± 0.9	NS

Data are means ± SE.

CONCLUSIONS — The insulin analog lispro, with a faster onset and a shorter duration of action compared with human insulin when given subcutaneously, has characteristics that make it superior in controlling postprandial blood glucose levels (11–17). However, overall blood glucose control has proved difficult to improve (21–25), perhaps partly because of higher late postprandial blood glucose concentrations (26,27). Higher nighttime glucose concentrations could also contribute to this difference and have been reported for other analogs (25,28), but this may only be advantageous in lowering the risk of much feared nighttime hypoglycemia.

In the present study, we compared the nighttime metabolic control achieved by type 1 diabetic patients when either lispro or human insulin was injected preprandially (before the evening meal). In order to avoid large interindividual differences in insulin sensitivity, we allowed only C-peptide–negative type 1 diabetic patients with good metabolic control to participate in the study.

The study confirmed that in type 1 diabetic patients, whether on a premeal plus basal insulin regimen or a twice-daily insulin regimen, premeal subcutaneous injection of lispro resulted in better postprandial blood glucose control compared with human insulin, as reported previously (16,21,26, 29–32). The difference in postprandial blood glucose excursions between lispro and human insulin would have been smaller if

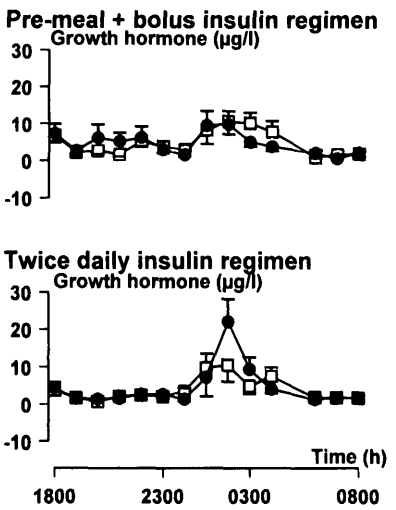

Figure 3—*Evening and nighttime (6:00 P.M. to 8:00 A.M.) plasma growth hormone concentrations (means ± SE) in patients using the premeal plus basal insulin or twice-daily insulin regimen after subcutaneous injection of unmodified human insulin (□) or lispro (●).*

human insulin had been injected 30 min before the meal (33,34), but in the present study, it was injected 5 min before the meal so as to make the study double-blind and closer to normal patient practice (35).

In patients on the premeal plus basal insulin regimen, nighttime (midnight to 4:00 A.M.) blood glucose levels were significantly higher after lispro than after unmodified human insulin. This appears to be due to hypoinsulinemia from 10:00 P.M. or earlier, as blood glucose concentrations are rising quickly by this time (Fig. 1) (7,8).

In patients on the twice-daily insulin regimen, the nighttime blood glucose profile after lispro was not different from that using unmodified insulin, perhaps because of a more dominant role for the extended-acting preparation when injected earlier in the evening. In previous studies, it has been demonstrated that preprandial injection of lispro and NPH together improves postprandial blood glucose control for up to 7 h after the meal in contrast to preprandial injection of either human insulin or lispro separately (26,27). Thus, for the twice-daily regimen, the present study is consistent with earlier studies that lispro therapy results in comparable overall blood glucose control despite improved postprandial blood glucose (24,36,37).

There was no significant difference in the incidence of hypoglycemia during the postprandial period (6:00–10:00 P.M.) after lispro therapy compared with unmodified human insulin, but the difference (6 vs. 2 events) suggests the possibility of a type 2 statistical error due to low study power, and the study design (in excluding patients having hypoglycemia before midnight) may have biased these results.

Importantly, the incidence of nighttime (midnight to 4:00 A.M.) hypoglycemia was significantly lower after lispro compared with human insulin. This occurred at a time when the blood glucose concentrations were significantly higher after lispro compared with human insulin therapy (Table 2). Previous reports have shown a small overall reduction in the incidence of hypoglycemia in patients receiving lispro (21–23,29,32, 38,39), with a lower rate of nocturnal hypoglycemia in patients on lispro compared with human insulin (32,38,40).

This study also demonstrated that, in patients on a premeal plus basal insulin regimen, there is relative hyperketonemia in addition to hyperglycemia in the early part of the night after lispro therapy, but this does not occur after unmodified human insulin. Such observations were not seen in patients on the twice-daily insulin regimen, consistent with the blood glucose results. Hyperglycemia and hyperketonemia were noted previously in the late postprandial period (3–7 h) after lispro therapy and were not found when NPH was injected at the same time as preprandial lispro (26).

In summary, the present study demonstrated that premeal lispro resulted in improved postprandial glycemic control and reduced blood glucose excursions. This was achieved when patients were receiving lispro therapy immediately before meals, demonstrating more flexibility in lispro therapy. More importantly, lispro therapy reduced the incidence of nocturnal hypoglycemia without disturbance of overall blood glucose control. Accordingly, lispro may be the ideal premeal insulin therapy for patients with recurrent early nocturnal hypoglycemia, able to ease fears of the most unwanted side effect of insulin therapy. However, this is at the expense of hyperglycemia and hyperketonemia in the early part of the night.

It may be that with optimization of mealtime and basal insulin doses (possibly less lispro and more NPH insulin), those patients not prone to nighttime hypoglycemia may be able to gain an overall improvement in blood glucose control when using fast-acting insulin analogs (41,42). With optimal basal insulin replacement to adapt for the fast-action properties of lispro, it may be possible to improve the postprandial, nighttime, and morning blood glucose profile and to abolish the nighttime hyperketonemia and, thus, improve the overall blood glucose control. As a consequence, more precise adjustment of optimal basal insulin replacement might further improve the overall blood glucose control and improve the average HbA1c without masking the positive effects of lispro in improving postprandial blood glucose control and reducing the incidence of hypoglycemia, particularly nocturnal hypoglycemia.

Acknowledgments — This work was supported by a grant from Eli Lilly, Basingstoke, U.K.

The authors gratefully acknowledge the dedicated assistance of M. Miller, M. Daley, B. Bulwer, L. Barriocannal, and E. Mason.

References

1. Frier BM: Hypoglycaemia in diabetes mellitus. In *Textbook of Diabetes*. 2nd ed. Pickup JC, Williams G, Eds. Oxford, U.K., Blackwell Science, 1997, p. 40.1–40.23
2. Bolli GB, Pirriello G, Fanelli CG, De Feo P: Nocturnal blood glucose control in type I diabetes mellitus. *Diabetes Care* 16 (Suppl. 3):71–85, 1993
3. Pramming S, Thorsteinsson B, Bendtson I, Ronn B, Binder C: Nocturnal hypoglycaemia in patients receiving conventional treatment with insulin. *Br Med J* 291:376–379, 1985
4. Home PD: Insulin therapy. In *International Textbook of Diabetes Mellitus*. 2nd ed.. Alberti KGMM, De Fronzo RA, Zimmet P, Eds. Chichester, U.K., Wiley, 1997, p. 899–928
5. Roy B, Chou MCY, Field JB: Time-action characteristics of regular and NPH insulin in insulin-treated diabetics. *J Clin Endocrinol Metab* 50:475–480, 1986
6. Owens DR: *Human Insulin: Clinical Pharmacology Studies in Normal Man*. Lancaster, PA, MTP Press, 1986, p. 46–70
7. 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 mealtime dose. *Metabolism* 30:439–442, 1981
8. 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
9. Heinemann L, Richter B: Clinical pharmacology of human insulin. *Diabetes Care* 16 (Suppl. 3):90–99, 1993
10. Heine RJ, Bilo HJG, Fonk T, van der Veen EA, van der Meer J: Absorption kinetics and action profile of mixtures of short- and intermediate-acting insulin. *Diabetologia* 27:558–562, 1984
11. Barnett AH, Owen DR: Insulin analogues. *Lancet* 349:47–51, 1997
12. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR: [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 43:396–402, 1994
13. Heinemann L, Starke AAR, Heding L, Jensen I, Berger M: Action profiles of fast onset insulin analogues. *Diabetologia* 33:384–386 1990
14. 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
15. Betz JL: Fast-acting human insulin analog: a promising innovation in diabetic care. *Diabetes Educ* 21:195–200, 1995
16. Howey DC, Hooper SA, Bowsher RR:

[Lys(B28), Pro(B29)]-human insulin: an equipotent analog of human insulin with rapid onset and short duration of action (Abstract). *Diabetes* 40 (Suppl. 1):423A, 1990
17. Ter Braak EW, Bianchi R, Erkelens DW: Faster, shorter, and more profound action of Lys(B28)Pro(B29) human insulin analogue compared to regular insulin irrespective of the injection site (Abstract). *Diabetes* 42 (Suppl. 1):207A, 1993
18. 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, 1988
19. Soeldner JS, Slone D: Critical variables in the RIA of serum insulin using the double antibody technique. *Diabetes* 14:771–779, 1965
20. 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
21. Kustner E, Frost T, Pfutzner A, Trautmann M, Beyer J: Insulin lispro improves blood glucose control without increase in the frequency of hypoglycaemia (Abstract). *Diabetologia* 38 (Suppl. 1):A190, 1995
22. Anderson JH, Brunelle RL, Vignati L: Insulin lispro improves postprandial glucose control and reduced hypoglycaemia rate in type 1 diabetes (Abstract). *Diabetologia* 38 (Suppl. 1):A3, 1995
23. Garg S, Carmain JA, Braddy KC, Jennings MK, Chase HP: Premeal insulin analog (Lys-Pro) vs. human regular insulin treatment in young type 1 diabetes (Abstract). *Diabetes* 43 (Suppl. 1):162A, 1994
24. Vignati L, Brunelle RL: Treatment of 722 patients with type II diabetes with insulin lispro in a 6-month crossover study (Abstract). *Diabetes* 44 (Suppl.1):229A, 1995
25. Nielsen FS, Jorgensen LN, Ipsen M, Voldsgaard AI, Parving HH: Long-term comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen. *Diabetologia* 38:592–598, 1995
26. 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
27. Torlone E, Pampanelli S, Lalli C, Di Vincenzi A, Epifano L, Rambotti AM, Kasso G, Brunetti P, Bolli GB: Postprandial glycemic control in IDDM after s.c. LysPro insulin analogue or human regular insulin, alone or mixed with NPH (Abstract). *Diabetes* 44 (Suppl. 1):71A, 1995
28. Jorgensen LN, Ipsen M, Voldsgaard AI, Nielsen FS: Comparison of human insulin analogue B10Asp and regular insulin in insulin-dependent diabetic patients on basal/bolus insulin regimen (Abstract). *Diabetes* 40 (Suppl. 1):464A,1990
29. Trautmann ME: Effect of the insulin analogue [Lys(B28), Pro(B29)] on blood glucose control. *Horm Metab Research* 26:588–590, 1994
30. Heinemann L, Heise T, Wahl LCh, 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(B29)] human insulin. *Diabet Med* 13:625–629, 1996
31. Pampanelli S, Torlone E, Lalli C, Del Sindaco P, Cioffetta M, Lepore M, Bartocci L, Brunetti P, Bolli G: Improved postprandial metabolic control after subcutaneous injection of a short-acting insulin analog in IDDM of short duration with residual pancreatic B-cell function. *Diabetes Care* 18: 1452–1460, 1995
32. Anderson JH Jr, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 46:265–270, 1997
33. Dimitriadis G, Gerich J: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 6:374–377, 1985
34. Lean MEJ, Ng LL, Tennison BR: Interval between insulin injection and eating in relation to blood glucose control in adult diabetics. *Br Med J* 290:105–108, 1985
35. Jorgensen LN, Nielsen FS: Timing of premeal insulins in diabetic patients on a multiple daily injection regimen: a questionnaire study (Abstract). *Diabetologia* 33:A116, 1990
36. Pieber TR, Feinbock C, Rabensteiner D, Weitgasser R, Ristic S: Lispro insulin analog in twice-a-day insulin treatment (Abstract). *Diabetologia* 38 (Suppl. 1):A3, 1995
37. Vignati L, Anderson JH, Szwast S, Symanowski S: Twice daily lispro results in less glucose variability compared to human regular insulin (Abstract). *Diabetologia* 38:A190, 1995
38. Brunelle RL, Symanowski S, Anderson JH Jr, Vignati L: Less nocturnal hypoglycemia with insulin lispro in comparison to human regular (Abstract). *Diabetes* 44 (Suppl. 1):111A, 1995
39. Short R: Nighttime hypoglycaemia. *Lancet* 359:1628–1629, 1995
40. Holcombe J, Zalani S, Arora V, Headlee S, Gill A: Insulin lispro (LP) results in less nocturnal hypoglycemia compared with regular insulin in adolescents with type 1 diabetes (Abstract). *Diabetes* 46 (Suppl. 1):103A, 1997
41. Jansson PA, Ebeling P, Smith U, Conget I, Coves M, Gomis R, Lalli C, Bolli G, Koivisto V: Glycemic control in IDDM is improved by optimized combination of insulin lispro and basal insulin (Abstract). *Diabetes* 46 (Suppl. 1):162A, 1997
42. Del Sindaco P, Ciofetta M, Lalli C, Torlone E, Perriello G, Brunetti P, Bolli G: Importance of basal insulin to improve control without increasing hypoglycaemia in intensively treated IDDM using a short-acting insulin analog at meals (Abstract). *Diabetologia* 40 (Suppl. 1):352A, 1997