Optimization of Evening Insulin Dose in Patients Using the Short-Acting Insulin Analog Lispro

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

OBJECTIVE — A three-way, crossover, open-label, randomized study was designed to compare the evening and night (1800–0800) glycemic control when the evening premeal lispro dose was reduced by 20% and the bedtime basal NPH dose increased by 25%, or when the basal NPH dose was moved to before dinner at 1800, compared with the control arm on standard premeal human regular insulin and pre-bedtime NPH insulin.

RESEARCH DESIGN AND METHODS — A total of 13 type 1 diabetic patients who use a premeal plus basal insulin regimen were studied on three separate days, with identical meals and snacks at the same times on each study day. On the control study day, patients received human regular insulin before dinner and NPH at bedtime in their usual doses. On another day, lispro was given before dinner with a dose reduction of 20%, and NPH at bedtime at 125% of usual dose. In the third regimen, the lispro and NPH were administered together in their usual dose before the evening meal by separate injections. The three regimens were tested in random order.

RESULTS — Postprandial (1800–2200) blood glucose concentrations were lower after reduced-dose lispro compared with human regular insulin (6.0 ± 0.3 [SEM] vs. 7.4 ± 0.3 mmol/l, $P < 0.05$). Nighttime (2400–0400) blood glucose concentrations were not different (8.6 ± 0.3 vs. 9.2 ± 0.3 mmol/l, NS), and prebreakfast concentrations were also unchanged (7.7 ± 0.9 vs. 8.7 ± 0.8 mmol/l) after lispro with increased-dose NPH compared with standard insulin. By contrast, both nighttime (10.0 ± 0.3 mmol/l, $P < 0.05$) and fasting glucose concentrations (10.8 ± 0.6 mmol/l, $P < 0.05$) were significantly higher with dinnertime usual-dose lispro plus dinnertime usual-dose NPH compared with standard human insulin. Hypoglycemia at night (blood glucose <3.0 mmol/l) did not differ between study days, but it was more frequent postprandially after dinner usual-dose lispro plus early NPH (2 vs. 7 patients, $P = 0.062$).

CONCLUSIONS — With lower mealtime and higher basal bedtime insulin doses, patients using insulin lispro may be able to gain an overall improvement in evening blood glucose control without deteriorated nighttime glucose levels. Earlier basal NPH dosage alone does not ameliorate the nighttime hyperglycemia of short-acting insulin analog regimens.

Insulin lispro is a genetically engineered analog of human insulin with a rapid onset and a shorter duration of action than human regular insulin (1–3). Insulin regimens based on the rapid-acting insulin analog lispro achieved better postprandial blood glucose control (4–11) and reduced the incidence of hypoglycemia (7–11), but improvement in overall blood glucose control has proved difficult to demonstrate (7–10). At least in part, this difficulty has been shown to be due to higher blood glucose levels in the early part of the night, as confirmed in detailed clinical studies in which the lispro regimen also gave significantly less nighttime hypoglycemia (10,11).

The present study was designed to build on those observations by asking whether the advantage of postprandial control could be maintained, and the early night hyperglycemia ameliorated, by decreasing the lispro dose and increasing the bedtime NPH dose. As blood glucose escape from lispro was evident as early as 4 h after injection (11), the effect of moving NPH dose to the time of the evening meal was also investigated.

RESEARCH DESIGN AND METHODS

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

Patients

Thirteen 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 approved by the local ethics committee.

All patients were normally using a premeal plus basal insulin regimen with human regular insulin before each meal and NPH insulin at bedtime. All patients had been stable on insulin for more than 1 year and had a mean HbA_{1c} of 7.4 ± 0.6% (SD) (normal <6.1%) and no serious hypoglycemic events. All patients had 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 3 separate days, at a 1- to 4-week interval, in random order. One to three 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

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 8 December 1997 and accepted in revised form 19 March 1998.

P.D.H., on behalf of the University of Newcastle-upon-Tyne, provides consultant services to and receives research support from all the major commercial insulin manufacturers. A.B.E.A.'s salary is at present paid from an Eli Lilly grant.

Table 1—*Characteristics of the type 1 diabetic patients studied*

n	13
Sex (M/W)	9/4
Age (years)	36 ± 12
Weight (kg)	72 ± 10
BMI (kg/m^2)	25.6 ± 2.7
C-peptide (nmol/l)	0.09 ± 0.05
HbA_{1c} (%) (normal <6.1%)	7.4 ± 0.6
Duration of diabetes (years)	11 ± 9
Evening regular insulin dose (U)	12 ± 4
Evening basal insulin dose (U)	20 ± 5

Data are means ± SD.

Table 2—*Summary of insulin regimens used on the 3 study days*

	Mealtime insulin			Basal insulin		
Protocol arm	Time	Insulin	Dose	Time	Insulin	Dose
Standard insulin	1755	Human	Usual	2200	NPH	Usual
Lispro optimized	1755	Lispro	80%	2200	NPH	125%
Early basal	1755	Lispro	Usual	1755	NPH	Usual

investigation unit at 1700 for overnight 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; patients whose blood glucose concentrations were not between 4.0 and 12.0 mmol/l at 1700 or whose blood glucose concentrations were more than 2.5 mmol/l different on study day 2 or 3 from study day 1 were asked to return another day.

Patients had an evening meal from a choice of foods at 1800. The choice and amount were recorded, and identical meal and snacks were then given at the same time on all study days. Five minutes before the evening meal, patients received a subcutaneous injection of the study insulin analog lispro (Humalog; Eli Lilly, Indianapolis, IN) on two 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 injections were given in a single-blind manner according to a randomization schedule.

The dose of lispro administered before the evening meal was reduced by 20% of the patient's usual premeal insulin dose at that time on one of study days (to 10 ± 3 [SD] U) and was the patient's usual premeal insulin dose at that time on the other day (12 ± 4 U; Table 2). With the reduced dose of premeal lispro, patients had an optimized dose of extended-acting NPH insulin at 2200 (25 ± 6 U), which was 125% of the patient's usual basal insulin at that time. With the usual dose of premeal lispro, patients had their usual dose (20 ± 5 U) of basal NPH insulin moved to before dinner at 1755 and given by separate injection. On the control study day, patients received human regular insulin before the evening meal (12 ± 4 U) and basal NPH insulin at bedtime (20 ± 5 U) in their usual doses (Table 2). On all three study days, the NPH insulin was injected into the anterior abdominal wall of the periumbilical region.

Venous blood samples for measurement of blood glucose, plasma free insulin, and blood intermediary metabolites concentrations were obtained at 1730, every 30 min until 2000, and then hourly until 0800. 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 or developed restlessness plus biochemical hypoglycemia during sleep. The blood glucose level for biochemical hypoglycemia was set as <3.0 mmol/l. Symptomatic hypoglycemia or restlessness plus hypoglycemia during sleep 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 Instrument 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 was prepared immediately after venipuncture and mixed with an equal volume of 30% polyetheylene glycol and centrifuged immediately (12). Plasma free insulin was measured by radioimmunoassay (13), using insulin or lispro standards as appropriate. Serum C-peptide was measured by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (DAKO C-peptide; DAKO, Ely, U.K.). Blood intermediary metabolites were measured as previously described (14).

Statistical analysis

All data were entered into a computer database and checked for correct entry. Results are expressed as means ± SEM unless stated otherwise. A P value <0.05 was considered statistically significant. The blood glucose concentrations at each time point were plotted for the three 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. The primary period for the present study was set as 2400–0400 in line with the earlier study (11), with the secondary period being 1800–2200 together with prebreakfast blood glucose levels. Statistical comparison between the three treatments was performed using analysis of variance for repeated measures with post hoc application of Student's Newman-Keuls test for multiple comparisons. Individual pairs of treatment points of interest were analyzed by Student's paired t tests.

Biochemical hypoglycemia (blood glucose level <3.0 mmol/l), 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's test. Other data are reported as a matter of observation only.

RESULTS

Blood glucose concentrations

Evening (1800–2200). Baseline blood glucose concentrations before the evening meal at 1800 were comparable on the three study days (Table 3, Fig. 1).

Postprandial blood glucose concentrations (1800–2200) were significantly lower after reduced lispro compared with standard regular insulin and after usual dose of lispro with early NPH dose compared with standard regular insulin (Table 3, Fig. 1). There was no significant difference in postprandial glucose concentration between the reduced and usual lispro dose.

Inspection of the blood glucose profiles (Fig. 1) shows lower postprandial glucose

Table 3—*Blood glucose concentrations (mmol/l) after standard human regular insulin regimen, reduced lispro with optimized NPH, and usual lispro with early NPH*

	Standard	Optimized basal	Early basal
Baseline (1800)	6.2 ± 0.6	6.3 ± 0.8	6.1 ± 0.8
Postprandial (1800–2200)	7.4 ± 0.3	6.0 ± 0.3*	5.5 ± 0.3*
Nighttime (2400–0400)	9.2 ± 0.3	8.6 ± 0.3	10.0 ± 0.3*†
Early morning (0400–0800)	8.5 ± 0.4	7.8 ± 0.5	10.6 ± 0.3*†
Fasting (0800)	8.7 ± 0.8	7.7 ± 0.9	10.8 ± 0.6*†

Data are means ± SEM. *$P < 0.05$ compared with standard regular insulin regimen; †$P < 0.05$ compared with optimized lispro and basal NPH insulin regimen.

concentrations from 1830 with both the reduced and normal lispro doses, converging again by 2200–2300. The 2-h postprandial blood glucose concentration at 2000 was significantly lower after lispro, reduced or usual dose, compared with standard regular insulin, but there was no difference in 2-h postprandial glucose concentration between reduced or usual dose of lispro (Table 3).

In the postprandial period (1800–2200), blood glucose fell to hypoglycemic levels (blood glucose <3.0 mmol/l) in two patients on standard regular insulin, four patients on the reduced-dose lispro dose (NS), and seven patients on the usual dose of lispro with early NPH dose (2 vs. 7 patients, $P = 0.062$, NS).

Nighttime. Early night (2400–0400) blood glucose concentration was not different after reduced-dose lispro with optimal NPH dose compared with standard regular insulin. The early night (2400–0400) glucose concentration was higher for the usual dose of lispro with early NPH compared with standard regular insulin or with the lispro with optimized basal regimen (Table 3, Fig. 1).

Inspection of the blood glucose profile shows that blood glucose concentrations rose to a plateau beginning at 0100 on the usual dose of lispro with early NPH and that the difference persisted throughout until the morning, with significantly higher prebreakfast glucose levels compared with either standard regular insulin or optimized lispro with NPH regimen (Table 3, Fig. 1). On the standard regular insulin and the reduced lispro with optimal NPH regimens, the nighttime blood glucose profiles were indistinguishable from 2200 onwards (Fig. 1). The apparent lower mean prebreakfast glucose level with the optimized regimen was not statistically significantly different from the prebreakfast glucose level with the standard regular insulin regimen (Table 3, Fig. 1).

Blood glucose concentrations fell to hypoglycemic levels in two patients on standard regular insulin and three patients on reduced lispro with optimal NPH in the early night (2400–0400) but in no patient on the usual dose of lispro with early NPH (all comparisons NS).

Plasma free insulin

Plasma free insulin concentrations before the evening meal at 1800 were comparable on the 3 study days (Table 4, Fig. 1).

Postprandial insulin concentrations (1800–2200) were significantly higher after lispro, reduced or usual dose, compared with standard regular insulin. The apparently lower postprandial insulin concentration after the reduced lispro dose compared with the usual lispro dose with early NPH was not statistically significant (Table 4, Fig. 1).

After lispro injection, plasma insulin concentrations declined rapidly from 1 h after injection, but stabilized from 2200 only

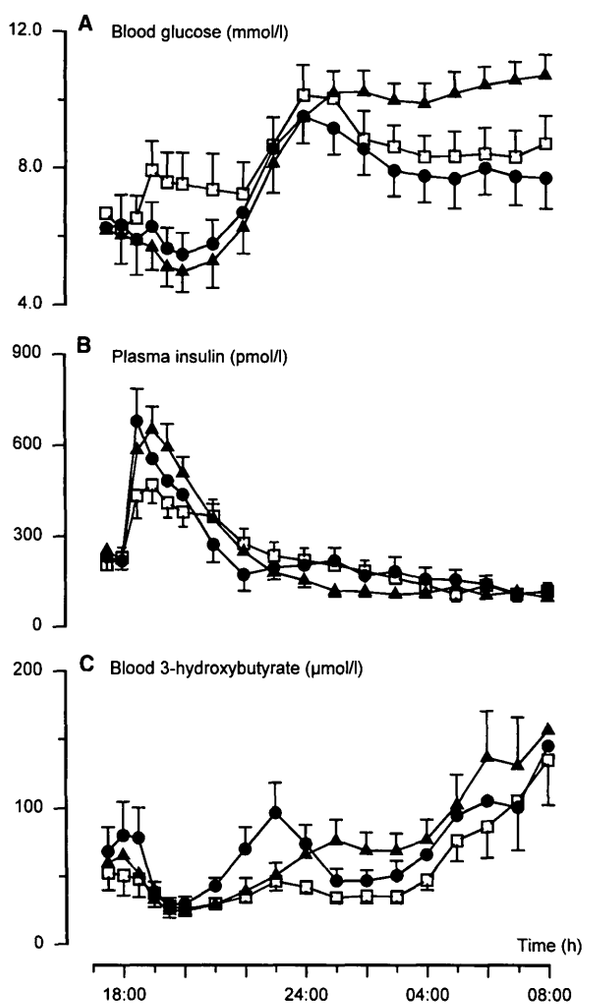

Figure 1—*Evening and nighttime blood glucose (A), plasma free insulin (B), and blood 3-hydroxybutyrate concentrations (C) (means ± SEM) in type 1 diabetic patients after subcutaneous injection of premeal insulin lispro in a reduced dose with evening NPH in an increased dose (●), lispro in a usual dose with an early basal NPH dose (▲), or standard premeal human regular insulin and evening basal NPH in usual doses (□).*

Table 4—*Plasma free insulin concentrations (pmol/l) after standard human regular insulin regimen, reduced lispro with optimized NPH, and usual lispro with early NPH insulin*

	Standard	Optimized basal	Early basal
Baseline (1800)	230 ± 33	219 ± 29	221 ± 29
Postprandial (1800–2200)	390 ± 24	486 ± 35*	539 ± 33*
Peak insulin concentration	482 ± 72	773 ± 80*	781 ± 61*
Nighttime (2400–0400)	180 ± 18	187 ± 18	120 ± 8*†
Fasting (0800)	119 ± 27	116 ± 27	98 ± 11

Data are means ± SEM. *$P < 0.05$ compared with standard regular insulin regimen; †$P < 0.05$ compared with optimized lispro and basal NPH insulin regimen.

on the increased NPH regimen (Fig. 1). In the early NPH regimen, insulin concentrations fell to levels of ~50% of baseline (1800) concentrations, which was significantly lower than for the other two regimens for the 2400–0400 period (Table 4, Fig. 1).

Blood intermediary metabolites

Blood lactate, pyruvate, and alanine concentrations and profiles did not differ between reduced lispro with optimal NPH or usual dose of lispro with early NPH dose and standard insulin (data not shown).

Blood 3-hydroxybutyrate levels were suppressed from mealtime until 2100 with all three insulin regimens. With reduced lispro and increased dose of basal NPH insulin, blood 3-hydroxybutyrate levels rose steadily from 2000 to peak at 2300 and declined again, escaping by the end of the night (Fig. 1). However, the levels achieved at all times were within physiological limits (normal fasting <400 μmol/l; Fig. 1). Higher nighttime (2400–0400) blood 3-hydroxybutyrate concentrations were noted on the lispro plus early basal NPH regimen compared with standard regular insulin (71 ± 6 vs. 39 ± 11 μmol/l, $P = 0.018$; Fig. 1), but nighttime (2400–0400) blood 3-hydroxybutyrate levels after the optimized regimen were not significantly different from the levels after standard regular insulin (57 ± 7 vs. 39 ± 11 μmol/l, NS; Fig. 1). Prebreakfast concentrations were identical for the three regimens.

CONCLUSIONS — In the present study, we assessed the nighttime glycemic control achieved by type 1 diabetic patients using a premeal plus basal insulin regimen who received a reduced dose of insulin lispro before the evening meal with increased basal NPH insulin at bedtime, or the usual premeal lispro dose together with earlier basal NPH dose before the evening meal, compared with a standard human insulin regimen. Only C-peptide–negative type 1 diabetic patients with preceding good metabolic control participated in the study, to avoid large interindividual differences in insulin sensitivity. A crossover design, limits on blood glucose concentrations at baseline, and strict standardization of meal content all serve to maintain statistical power in a small and intensive overnight study.

The reduction of lispro dose (20%) was chosen on the basis that postprandial glucose control would remain improved, given that previous studies at unchanged dose resulted in considerable biochemical hypoglycemia (11,15) with likely counterregulatory hormone effects and that other clinical laboratory studies have suggested that lispro dose preprandially may be too high (3,15). The present study confirms that postprandial glycemic control is maintained with the reduced dose of lispro, and indeed was no worse than when a usual dose of lispro was combined with mealtime NPH (Table 3, Fig. 1). The design of the study might be thought to give favorable results for insulin lispro, as human regular insulin was not given 30 min or more before the evening meal. From the pharmacokinetic point of view, there may be an advantage for an injection-meal interval (16–18) due to the slow absorption of human insulin after subcutaneous injection (19–21). 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 (22–25). The present study was therefore performed under conditions close to normal patient practice.

Our previous study (11), consistent with the published clinical studies, clearly demonstrated that an increased dose of the evening basal extended-acting NPH insulin would be needed to prevent the deterioration of glucose levels found on short-acting insulin analog regimens after midnight. The increase of 25% proved able to prevent any such early nighttime or prebreakfast deterioration, and indeed, if anything, glucose levels were lower on the optimized lispro and basal insulin regimen than on human insulin regimen. It is important to emphasize that the optimization of the insulin dose with 20% reduction of the premeal insulin (lispro) dose and 25% increase in the evening basal (NPH) insulin dose had resulted in an absolute increase of 3 U in the total evening insulin dose. These results are consistent with previously reported results that demonstrated an improvement in the overall blood glucose control with an optimal increase in the basal insulin dose and a reduction in the premeal lispro dose (26). Although biochemical hypoglycemia was not a problem with the optimized basal regimen in this study, this study could not have the power to address that question adequately. Meanwhile, given that the absorption of NPH insulin is known to be erratic, further increase (on average) in evening NPH dosage does not appear advisable.

Previous studies demonstrated that insulin lispro improves early as well as late postprandial glucose control for up to 8 h after insulin injection when extended-acting insulin (NPH or human ultralente) is injected at the same time as premeal insulin lispro (4,5). This provided the basis for the second part of the present study, as a sharp deterioration in blood glucose concentrations had been noted as early as 2200 on the short-acting insulin analog regimen (11), as confirmed in the present study (Fig. 1). When the usual lispro dose and NPH were injected together before the evening meal, the 2200–2400 deterioration in glucose control was not prevented (Fig. 1), and because of nighttime hypoinsulinemia (Table 4, Fig. 1), a greater degree of hyperglycemia was found from 0200 until the morning (Fig. 1). This indicates the importance of the timing as well as the dose of basal extended-acting insulin within a short-acting insulin analog regimen, and it remains untested whether the optimized basal dose and change in the timing of the dose together might not give an appropriate glucose profile.

In conclusion, the present study has demonstrated that the short-acting insulin analog lispro results in improved postprandial blood glucose control compared with human regular insulin, even when given at 80% of the usual premeal human insulin dose. More importantly, an insulin lispro regimen gives improved postprandial glucose control without deterioration in

the nighttime glycemic control if the basal insulin is optimally replaced at a higher dosage. Merely moving the basal extended-acting NPH insulin dose forward to the time of the evening meal is not a solution to the problem of nighttime hyperglycemia with an insulin analog regimen.

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

The authors gratefully acknowledge the dedicated assistance of E. Mason, M. Daley, S. Bennett, M. Brown, and M. Al-Maskari.

References

1. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR: Lispro human insulin: a rapidly absorbed analog of human insulin. *Diabetes* 43:396–402, 1994
2. Heinemann L, Starke AAR, Heding L, Jensen I, Berger M: Action profiles of fast onset insulin analogues. *Diabetologia* 33:384–386, 1990
3. 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
4. Burge M, 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
5. 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
6. 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
7. Heinemann L, Heise T, Wahl LC, 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 insulin. *Diabet Med* 13:625–629, 1996
8. Carg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK, Chase HP: Pre-meal insulin analogue insulin lispro vs. Humulin R insulin treatment in young subjects with type 1 diabetes. *Diabet Med* 13:47–52, 1996
9. 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
10. 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
11. 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
12. 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
13. Soeldner JS, Slone D: Critical variables in the radioimmunoassay of serum insulin using the double antibody technic. *Diabetes* 14:771–779, 1965
14. 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
15. Burge MR, Castillo KR, Schade DS: Meal composition is a determinant of lispro-induced hypoglycemia in IDDM. *Diabetes Care* 20:152–155, 1997
16. 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
17. Dimitriadis G, Gerich J: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 6:374–377, 1985
18. 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
19. 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
20. 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
21. 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
22. 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
23. Berger M, Heinemann L: Are presently available insulin analogues clinically beneficial? (Letter) *Diabet Med* 40 (Suppl. 2):S91–S96, 1997
24. Heinemann L: Do insulin treated diabetic patients use an injection-meal interval in daily life? (Letter) *Diabet Med* 12:449–450, 1995
25. 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
26. Ebeling P, Jansson PA, Smith U, Lalli C, Bolli GB, Koivisto VA: Strategies toward improved control during insulin lispro therapy in IDDM: importance of basal insulin. *Diabetes Care* 20:1287–1289, 1997