Reduced Frequency of Severe Hypoglycemia and Coma in Well-Controlled IDDM Patients Treated With Insulin Lispro

FRITS HOLLEMAN, MD
HENRY SCHMITT, MD
RAOUL ROTTIERS, MD
ALAN REES, MD, FRCP
SHARON SYMANOWSKI, PHD
JAMES H. ANDERSON, MD
THE BENELUX-UK INSULIN LISPRO STUDY GROUP

OBJECTIVE — Several studies have suggested that use of the short-acting insulin analog, insulin lispro, in multiple injection therapy may reduce the risk of hypoglycemia in comparison with regular insulin. This effect might be more pronounced in well-controlled patients, since intensive treatment of IDDM increases the rate of severe hypoglycemic events. This study evaluated the effects of insulin lispro on glycemic control and hypoglycemia rates in well-controlled IDDM patients.

RESEARCH DESIGN AND METHODS — This was an open, randomized, 6-month crossover study of 199 IDDM patients. Glycemic control was evaluated by HbA_{1c}, home blood glucose measurements, and rate and timing of hypoglycemic events. At the end of the study, patients completed an evaluation form regarding therapy-related quality of life.

RESULTS — HbA_{1c} remained constant at ~7.3% throughout the study. Meal-related glucose excursions were significantly lower with insulin lispro compared with regular insulin (mean −0.8 ± 1.7 vs. 1.1 ± 1.6 mmol/l, $P < 0.001$), as was the within-day variability (M value 27.7 ± 19.7 vs. 30.2 ± 23.1, $P = 0.007$). The incidence of severe hypoglycemic events (58 vs. 36, $P = 0.037$) including coma (16 vs. 3, $P = 0.004$) was significantly lower with insulin lispro than with regular insulin. Patients felt that insulin lispro increased flexibility and freedom of lifestyle.

CONCLUSIONS — In well-controlled IDDM patients, insulin lispro is associated with a lower risk of severe hypoglycemia and coma.

Intensive treatment of diabetes reduces the risk of long-term complications such as retinopathy and nephropathy (1,2). The goals of intensive treatment are normoglycemia and normo-insulinemia. These goals are usually achieved by the use of either continuous subcutaneous insulin infusion (CSII) or multiple injection therapy (MIT) together with frequent home blood glucose monitoring.

The latter consists of intermediate-acting NPH insulin to mimic the physiological basal insulinemia and three or more dosages of the short-acting regular insulin imitating the meal-related insulin peaks (3).

However, MIT has some disadvantages. First, the NPH insulin does not work long enough to provide a stable basal insulinemia when injected once daily (4,5). Second, the regular insulin actually has a late onset of action (time to peak, about 2 h), leading to the necessity to inject the insulin one half hour before the meal as well as a long duration of action (4–6 h) leading to a risk of late postprandial hypoglycemia (5–7).

The risk of hypoglycemia during intensive therapy must not be underestimated. In the Diabetes Control and Complications Trial (DCCT), the incidence of severe hypoglycemia (defined by the necessity of third-party assistance) was three times higher in the intensively treated patients, compared with conventionally treated patients (2,8,9); an inverse relationship existed between overall glycemia as reflected in HbA_{1c} levels and hypoglycemia rates.

Severe hypoglycemia is associated with significant morbidity and ranks high in the fears of patients (10–12). Thus, attempts to improve glycemic control are primarily hampered by the increased hypoglycemia rate.

In the last few years, several insulin analogs with improved pharmacokinetic characteristics have been biosynthetically engineered (13–16). One of these is the LysB28,ProB29 human insulin analog (insulin lispro) (Humalog, Eli Lilly, Indianapolis, IN). It has a rapid onset of action (time to peak, <1 h) and a short duration of action (<4 h) (17). Results so far indicate that this analog is a safe and rational substitute for regular insulin in MIT (18–20). Moreover, some studies indicate that hypoglycemia rates are lower when using insulin lispro (19,21,22).

This study was designed to investigate whether MIT using insulin lispro and NPH insulin could improve glycemic control and/or hypoglycemia rates in already well-controlled IDDM patients.

RESEARCH DESIGN AND METHODS

Patients

The study was conducted in 19 centers in the U.K., Belgium, and the Netherlands. The study was not part of any of the previously published large-scale multinational trials of insulin lispro. Patients (age 18–65 years) were eligible for the study if they met the World Health Organization (WHO) criteria for IDDM. They were required to have

From Department of Internal Medicine (F.H.), Diakonessenhuis, Utrecht, The Netherlands; Eli Lilly (H.S., S.S., J.H.A.), Indianapolis, Indiana; University Hospital (R.R.), Gent, Belgium; and University Hospital Wales (A.R.), Cardiff, Wales, U.K.

Address correspondence and reprint requests to Frits Holleman, MD, Department of Internal Medicine, Diakonessenhuis, Bosboomstraat 1, 3582 KE Utrecht, The Netherlands. E-mail: fhollema@worldonline.nl.

Received for publication 18 June 1997 and accepted in revised form 20 August 1997.

Abbreviations: CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; MIT, multiple injection therapy.

Table 1—*Patient characteristics at randomization*

	All patients	Lispro-regular	Regular-lispro
n	199	96	103
Women	73 (37)	38 (40)	35 (34)
Men	126 (63)	58 (60)	68 (66)
Age (years)	35.4 ± 9.6	34.9 ± 9.6	35.9 ± 9.7
BMI (kg/m^2)	25.0 ± 3.1	25.2 ± 3.1	24.8 ± 3.2
Duration of diabetes (years)	13.1 ± 9.1	14.2 ± 9.9	12.0 ± 8.1
Hypoglycemia rate/30 days	5.7 ± 5.8	5.7 ± 6.2	5.7 ± 5.5
HbA_{1c} (%)	7.3 ± 1.1	7.4 ± 1.2	7.3 ± 1.0
Patients completing the study	189 (95)	91 (95)	98 (95)

Data are means ± SD or *n* (%).

been treated with insulin for at least a year and with MIT using regular insulin for the last 3 months; the HbA_{1c} level had to be within 1.5 times the top normal range of the local laboratory. Patients with a history of hypoglycemia unawareness and patients with more than two hospitalizations for hypoglycemia in the last year were excluded.

The trial was conducted in accordance with the Declaration of Helsinki and with European Good Clinical and Laboratory Practice (GCP/GLP) guidelines after approval by local ethics committees. Written informed consent was obtained before inclusion.

Study design

The trial had an open-label crossover design. The study started with a run-in period of 4 weeks, during which the treatment with regular insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark) in combination with NPH insulin (Insulatard or Protaphane, Novo Nordisk) was optimized. After this run-in period, patients were treated in a randomized order with insulin lispro (Humalog) in combination with NPH insulin (Humulin NPH, Eli Lilly) for 12 weeks and with regular insulin (Actrapid, Novo Nordisk) in combination with NPH insulin (Insulatard or Protaphane, Novo Nordisk) for 12 weeks. Study visits were scheduled at baseline, after the run-in period and after 4 and 12 weeks of each treatment.

Patients were instructed to inject regular insulin one half hour before meals and to inject insulin lispro immediately before meals. They were not allowed to change the injection sites during the study. Premeal insulin was adjusted in attempts to reach a target glucose value of ≤10 mmol/l 2 h postprandial; NPH insulin dose was adjusted to reach a target value of ≤7 mmol/l fasting. The use of a second injection of NPH insulin, although allowed if average glycemia before meals remained above 7.8 mmol/l, was discouraged.

In the last 2 weeks before each study visit, each patient recorded four 7-point home blood glucose monitoring profiles. The frequency and timing of food intake (meals and snacks) were also recorded on these 4 days. During the whole study period, patients noted time, severity, symptoms, and therapy of subjective and objective hypoglycemic events. Objective hypoglycemia was defined as a blood glucose value <3 mmol/l. Severe hypoglycemia was defined as an episode in which the patient was unable to treat him/herself and/or reported treatment with intravenous glucose or glucagon and/or reported coma.

At the end of the study, patients completed a therapy-related quality-of-life evaluation questionnaire.

Efficacy measures

Primary efficacy measures were HbA_{1c}, incidence and timing of hypoglycemic episodes, and home blood glucose measurements. The 2-h postprandial glucose excursions and within-day variability of glucose levels as reflected in the *M* value (23) were determined. The *M* value is defined as $\Sigma \{|10 \times \log_{10}(\text{blood glucose/standard value})|^3\} \div n$. The chosen standard euglycemic value for determination of the *M* value was 5.0 mmol/l. Additional efficacy measures included quality-of-life data, weight, dose of insulin, and number of snacks.

HbA_{1c} was measured in a central laboratory (SCICOR, Geneva, Switzerland) using a high-performance liquid chromatograph (HPLC) method (reference range 4.3–6.1%). Home blood glucose monitoring was performed using the Accutrend DM (Boehringer Mannheim, Brussels, Belgium).

The quality-of-life evaluation questionnaire consisted of 20 questions with 5-point scales. Patients were asked to rank insulin lispro versus regular insulin on a number of items such as general satisfaction, flexibility and freedom of life, quality of glycemic control, etc.

Statistical analysis

Data for the two treatment sequences were pooled. The efficacy analyses were performed on an intention-to-treat basis and included all available data from all randomized patients. An analysis for carry-over effects using the Koch model was performed before all treatment analyses. All treatment comparisons were performed using a two-tailed test with a nominal significance level of 0.05. Quality-of-life data were assessed using a nonparametric Sign test in which the number of patients expressing preference for insulin lispro was compared with the number expressing preference for regular insulin for each question.

RESULTS

Glycemic control

A total of 199 patients (126 men, 73 women) were randomized. Of the patients, 96 were randomized to the lispro-regular sequence group and 103 were randomized to the regular-lispro group. Baseline characteristics between the two sequence groups did not differ significantly (Table 1).

Of the patients, 189 completed both study periods; 6 patients withdrew because of perceived lack of efficacy of insulin lispro, 1 patient died of ischemic heart disease, and 2 patients were discontinued at their own/investigators' decision. One patient had a positive pregnancy test after 29 days use of insulin lispro and was discontinued from the study; she had an uneventful pregnancy and normal delivery.

Results of HbA_{1c} and 7-point home blood glucose measurements are presented in Table 2. HbA_{1c} levels were similar for both treatments. Meal-related glucose excursions were significantly lowered during insulin lispro treatment (mean excursion 1.1 ± 1.6 mmol/l for regular insulin and −0.8 ± 1.7 mmol/l for insulin lispro, $P < 0.001$). Predinner glucose was higher during treatment with insulin lispro (8.7 vs. 7.5 mmol/l, $P < 0.001$). The daily glucose variability, as expressed in the *M* value, was significantly lower for insulin lispro.

Table 2—*Results of home blood glucose measurements and HbA_{1c}*

	Baseline	After 12 weeks of treatment: Regular	Lispro	*P* value
HbA_{1c} (%)	7.3 ± 1.1	7.5 ± 1.2	7.6 ± 1.3	0.697
Fasting glucose	8.2 ± 2.3	8.9 ± 2.7	9.3 ± 2.6	0.083
2-h postbreakfast	9.2 ± 2.9	9.7 ± 3.2	7.7 ± 2.6	<0.001
Morning glucose excursion	0.9 ± 2.9	0.8 ± 3.0	−1.5 ± 2.8	<0.001
Prelunch glucose	6.6 ± 2.1	7.3 ± 2.5	7.2 ± 2.4	0.538
2-h postlunch	8.2 ± 2.6	8.6 ± 2.5	7.5 ± 2.3	<0.001
Lunch glucose excursion	1.5 ± 2.7	1.3 ± 2.5	0.3 ± 2.3	<0.001
Predinner glucose	7.6 ± 2.6	7.5 ± 2.6	8.7 ± 2.8	<0.001
2-h postdinner	8.4 ± 2.9	8.9 ± 3.1	7.7 ± 2.6	<0.001
Dinner glucose excursion	0.9 ± 2.8	1.3 ± 2.7	−1.0 ± 2.7	<0.001
Bedtime glucose	8.4 ± 2.7	8.7 ± 3.0	9.1 ± 2.7	0.215
Mean preprandial glucose	7.5 ± 1.7	7.9 ± 2	8.4 ± 1.9	0.001
Mean glucose excursion	1.1 ± 1.6	1.1 ± 1.6	−0.8 ± 1.7	<0.001
M value (daily glucose variability)	27.7 ± 17.2	30.2 ± 23.1	27.7 ± 19.7	0.007

Data are means ± SD. All measurements, except HbA_{1c} and *M* value, are given in millimoles per liter.

Data on hypoglycemic episodes are presented in Table 3. There was no difference in overall hypoglycemia rates. However, severe hypoglycemia (58 vs. 36 episodes, χ^2 test, $P = 0.037$) including coma (16 vs. 3 episodes, $P = 0.004$) were significantly reduced during treatment with insulin lispro.

Hypoglycemia occurred earlier after the administration of insulin lispro, compared with regular insulin (4.3 h vs. 5.2 h, $P < 0.001$). The frequency of nocturnal hypoglycemia was significantly decreased with insulin lispro, while the frequency of morning hypoglycemia increased. Likewise, most of the severe hypoglycemic episodes occurred during the night (second half), as can be seen in Figs. 1*A–C*. Data on the other efficacy measures are presented in Table 4.

The total doses of short-acting and long-acting insulin increased during the study. This effect was significantly more pronounced during treatment with insulin lispro. Nearly no patient received NPH insulin twice a day (mean number of basal doses 1.00 ± 0.02 for regular insulin and 1.01 ± 0.07 for insulin lispro, $P = 0.061$). Body weight increased more with regular insulin. No significant carry-over effects were observed.

Quality-of-life data

Of the patients, 189 completed the quality-of-life evaluation questionnaire, and 94% of patients indicated they injected insulin lispro within 10 min before the meal. In spite of the study instructions, 31% of patients injected regular insulin within 10 min, 34% injected regular insulin between 10 and 20 min, and only 27% injected regular insulin between 20 and 30 min before the meal. Patients expressed more flexibility in their lifestyle in general (86% as easier vs. 2% as more difficult, $P < 0.0001$), timing of meals (70 vs. 3%, $P < 0.0001$), planning of physical (51 vs. 9%, $P < 0.0001$) and social activities (60 vs. 8%, $P < 0.0001$) when using insulin lispro.

Of 199 randomized patients, 144 elected to continue treatment with insulin lispro. Their baseline characteristics did not differ from those who did not continue.

CONCLUSIONS — Because of the differences in time-action profiles between treatments, this study was not blinded. The data, especially those from the quality-of-life evaluation questionnaire, must therefore be interpreted with some caution. However, the randomized crossover design, which was carefully controlled for carry-over effects, allows some conclusions to be drawn.

From this study it is clear that insulin lispro leads to significant and impressive reductions in postprandial glucose excursions. Even though preprandial glucose values tended to increase during treatment with insulin lispro, the postprandial values were consistently lower during treatment with insulin lispro. In contrast, there was no difference in overall glycemic control, as reflected in HbA_{1c}. How can these data be reconciled?

Preprandial values rose more during treatment with insulin lispro, as did the bedtime value. This rise can only be explained by a relative lack of basal insulin between the meals. Given the short action profile of insulin lispro, it is not surprising that this effect is exacerbated by long intervals between meals, and is most pronounced late in the afternoon, before dinner, when the action of the NPH insulin of the evening before has ceased. The longer action of regular insulin compared with insulin lispro partially compensates for this lack of basal

Table 3—*Hypoglycemic events during the study periods*

	Total	Regular insulin	Insulin lispro	*P* value
Total	4,593	2,344	2,249	NS
Nonsevere				
Total	4,499	2,286	2,213	NS
Severe				
Total	94	58	36	0.037*
Coma	19	16	3	0.004*
Symptomatic				
Total	3,617	1,846	1,771	NS
<3.0 mmol/l	2,095	1,055	1,040	NS
Asymptomatic				
Total	976	498	478	NS
<3.0 mmol/l	924	479	445	NS
12:00–6:00 A.M.	488	312	176	<0.001†
6:00 A.M.–12:00 P.M.	1,395	612	783	0.015†
12:00–6:00 P.M.	1,510	790	720	NS
6:00 P.M.–12:00 A.M.	1,150	604	546	NS

Data are *n*. *χ^2 test; †χ^2 approximation to the Wilcoxon's rank-sum test

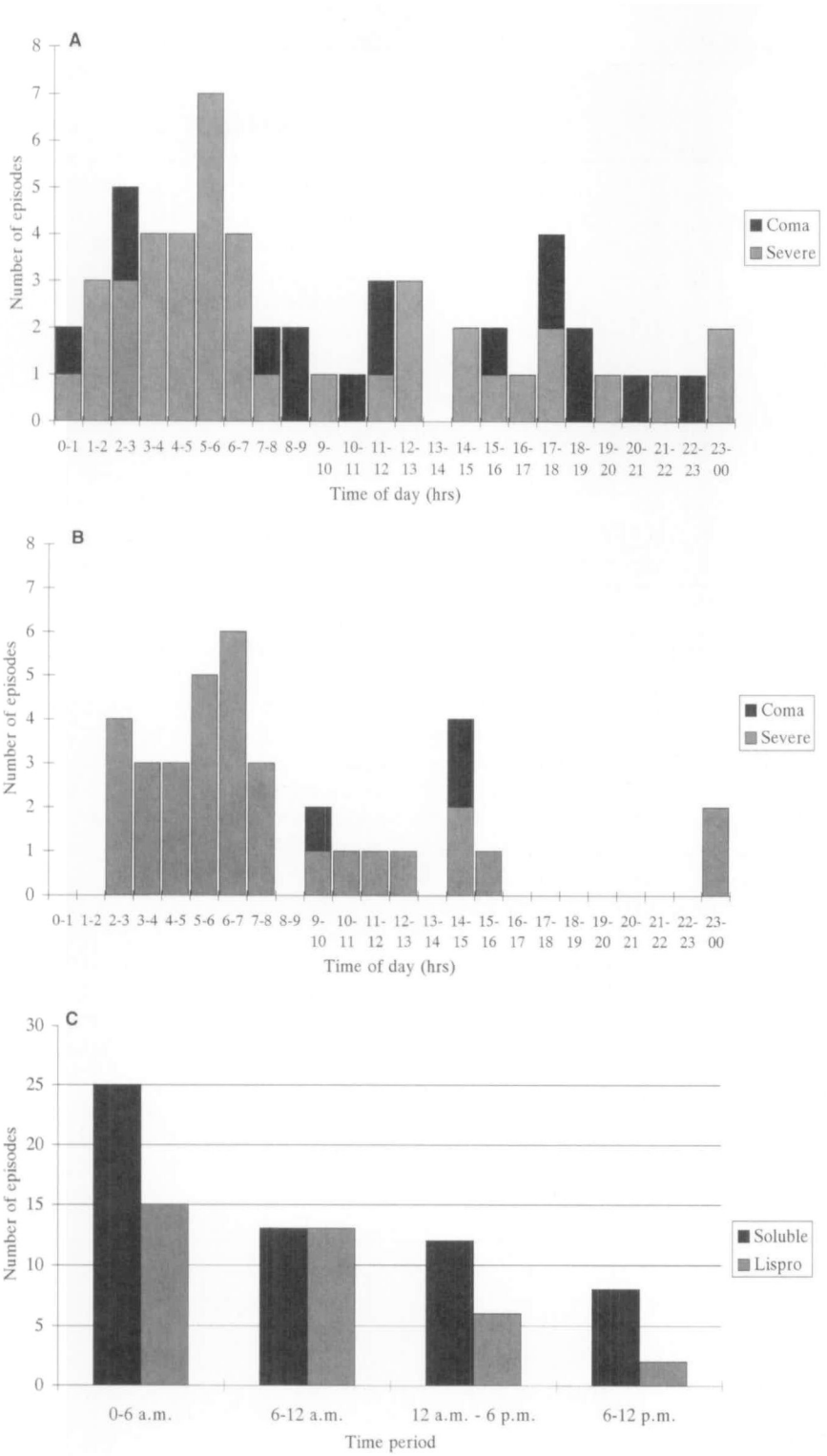

Figure 1—A: *the distribution of coma and severe hypoglycemia during treatment with regular insulin.* B: *the distribution of coma and severe hypoglycemia during treatment with insulin lispro. C: the distribution of severe hypoglycemia per period. Because of the small number of episodes, none of the differences reached statistical significance.*

insulin. Thus, the advantage of insulin lispro with respect to postprandial glucose excursions is, in our opinion, counterbalanced by a prolonged exposure to slightly higher glucose levels late in the afternoon and during the night, as demonstrated in Fig. 2.

The most important finding of our study was that treatment with insulin lispro was associated with a significant decrease in severe hypoglycemic episodes and coma in these well-controlled patients. However, the decrease in total number of hypoglycemic events was not significant. This paradox can be explained by the fact that, as in the DCCT, most of the severe hypoglycemic episodes occurred during the night (see Figs. 1*A–C*). Pramming et al. (24) have previously shown that most patients with biochemical hypoglycemia during the night do not wake up. Thus the risk of prolonged and severe hypoglycemia is increased during the night. The fact that we found less severe hypoglycemia is therefore in line with the reduced frequency of nocturnal hypoglycemia in our study (Table 3).

Since there are no differences in counterregulation or hypoglycemia awareness between insulin lispro and regular insulin (25–27), it seems unlikely that a difference in the occurrence of symptoms would have caused the lower incidence of nocturnal hypoglycemia with insulin lispro. In the study by Pramming et al. (24), higher bedtime and fasting glucose levels were associated with lower hypoglycemia rates. Again, we feel that slightly higher nighttime glucose levels with insulin lispro, which are the result of rapid weaning of the insulin effect, may have contributed to the observed difference between insulin lispro and regular insulin.

The initial rate of severe hypoglycemia in our study was 99/100 patient-years in patients with an average HbA_{1c} of 7.3%. This can well be compared with results reported by the DCCT (62/100 patient-years with average HbA_{1c} 7.1% [1]), the Stockholm Diabetes Intervention Study (110/100 patient-years with average HbA_{1c} 7.1% [2]), Macleod et al. (170/100 patient-years with average HbA_1 of 10.7% [10]), and Pramming et al. (140/100 patient-years with average HbA_{1c} of 8.7% [28]). As in the DCCT, ~30% of severe hypoglycemic events resulted in coma (8).

An interesting finding is that, in spite of specific instructions to inject regular insulin one half hour before the meal, a majority of the patients indicated that they failed to do so. Injection time instructions for insulin lispro, on the other hand, were followed. This may have biased the glucose excursions in favor of insulin lispro. However, since patients participating in studies are, in general, better motivated than the average patient, this underscores the fact that the rapid action profile of insulin lispro does indeed contribute to psychological freedom of lifestyle for the diabetic patient.

Table 4—*Other efficacy data*

	Baseline	After 12 weeks of treatment		P value
		Regular insulin	Insulin lispro	
Cumulative dose of insulin (IU)	53.2 ± 17.5	55.2 ± 19.1	57.8 ± 19.8	<0.001
Total dose of short-acting insulin/day (IU)	34.0 ± 11.9	35.6 ± 13.4	36.9 ± 14.2	0.04
Total dose of NPH/day (IU)	19.2 ± 8.4	19.7 ± 8.6	20.9 ± 8.8	<0.001
Body weight (kg)	75.0 ± 12.7	75.8 ± 13.0	75.3 ± 13.1	0.03
Number of snacks /day	1.9 ± 1.5	1.8 ± 1.8	1.9 ± 1.5	0.13

Data are means ± SD.

Lean et al.(7) and Jørgensen et al. (29) have previously reported on the low rate of compliance with injection instructions for regular insulin.

Finally, a tendency to increase the dosage of NPH insulin and short-acting insulin was noted during treatment with insulin lispro. However, the increase in weight was less with insulin lispro than with regular insulin. These facts and the improved *M* value suggest a more physiological balance between glucose intake and disposal with insulin lispro therapy.

The main problem of intensive therapy with insulin lispro and once-daily NPH insulin seems to be the relative lack of basal insulinemia in the afternoon and evening. Evidence for the role of basal insulinemia is given by a recent study of CSII with insulin lispro, which resulted in improved HbA_{1c}, while hypoglycemia rates were similar or even lower than with regular insulin (30). The problem of insufficient basal insulinemia can be addressed in several ways.

Some patients, especially those with high fasting glucose levels, may benefit from an increase in the evening dosage of NPH insulin. This possibly explains why we found an increase in NPH insulin dose. However, given the higher nighttime glycemia in our study, this solution was not always sufficient, possibly because patients feared that an increase in NPH insulin could paradoxically lead to late nocturnal hypoglycemia. A second option would be to diminish the consumption of snacks in the afternoon and evening. Improving diet behavior can significantly lower HbA_{1c} levels as shown in the DCCT (31). However, compliance may be difficult, and the increase in nighttime glucose levels (mainly caused by the endogenic hepatic glucose production) would not be affected.

The third and probably the most feasible option would be to give additional NPH insulin dosages. In a study of nine patients by Karşidag et al., the introduction of a second NPH insulin injection in an insulin lispro–based regimen led to a dramatic improvement in glycemic control (32). Torlone et al. have demonstrated that mixing insulin lispro with small doses of NPH insulin could solve the problem of basal insulinemia (33). As a sequel to our study, a properly designed study of lispro-based regimens with once- versus twice-daily NPH insulin injections might show whether improved nighttime glycemia can result in improved HbA_{1c} without losing the current benefit of less nighttime (severe) hypoglycemia.

Finally, a simpler option would be the introduction of a truly long-acting basal insulin analog which could replace NPH insulin. Several of these insulin analogs are being developed (34–36), but none is currently available for general use.

In conclusion, insulin lispro improves various parameters of glycemic control, such as meal-related glucose excursions, the *M* value, and the frequency of severe hypoglycemic episodes in well-controlled IDDM patients, without compromising their HbA_{1c} levels, weight, or insulin dose. The possibility to inject insulin lispro just before the meal contributes to patient convenience. Thus, insulin lispro offers several advantages over regular insulin in intensive treatment.

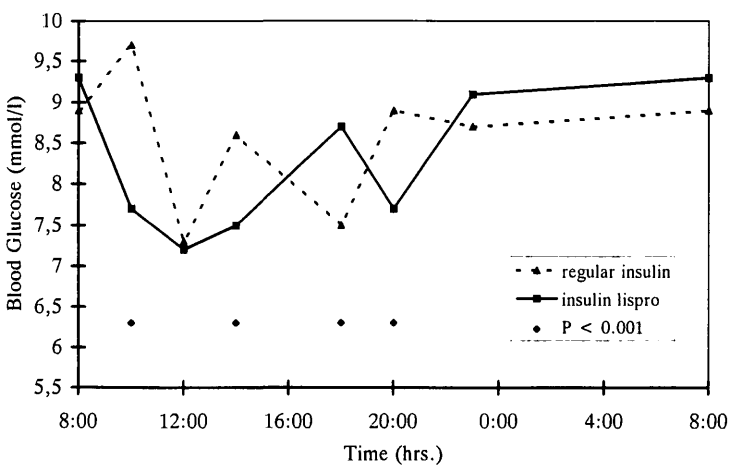

Figure 2—*Glucose profiles during treatment with insulin lispro compared with regular insulin.*

Acknowledgments— This work was financially supported by Eli Lilly and Company, Indianapolis, Indiana.

We thank Keith Gantner for his valuable help in the analysis of the data.

APPENDIX

The Benelux-UK insulin lispro study group

Belgium: P. van Crombrugge (Aalst), F. Fery (Brussels), L.F. van Gaal (Wilrijk), R. Rottiers (Gent), and G. Somers† (Brussels). The Netherlands: E. van Ballegooie (Zwolle), J.W.F. Elte (Rotterdam), J.B.L. Hoekstra, F. Holleman (Utrecht), and R.P.L.M. Hoogma (Gouda). U.K.: L.J. Borthwick (Stevenage), C. Fox (Northhampton), D. Gordon (Glasgow), R.J.C. Guy (Basingstoke), W.J. Jeffcoate (Nottingham), A.C. MacCuish (Glasgow), J. Peters, A. Rees (Cardiff), D.E. Price (Swansea), P. Price (Swindon), and G. Rayman (Ipswich).

†Deceased.

References

1. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U: Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the

Stockholm Diabetes Intervention Study (SDIS) after 5 years. *J Intern Med* 230:101–108, 1991
2. The Diabetes Control and Complications Trial 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* 329:977–986, 1993
3. Zinman B: Insulin regimens and strategies for IDDM: *Diabetes Care* 16 (Suppl. 3):24–28, 1993
4. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 7:188–199, 1984
5. Heinemann L, Richter B: Clinical pharmacology of human insulin. *Diabetes Care* 16 (Suppl. 3):90–100, 1993
6. Dimitriadis GD, Gerich JE: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 6:374–377, 1983
7. 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
8. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 90:450–459, 1991
9. The Diabetes Control and Complications Trial Research Group: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 18:1415–1427, 1995
10. Macleod KM, Hepburn DA, Frier BM: Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. *Diabet Med* 10:238–245, 1993
11. Wredling RAM, Töres Theorell PG, Roll HM, Lins PES, Adamson UKC: Psychosocial state of patients with IDDM prone to recurrent episodes of severe hypoglycemia. *Diabetes Care* 15:518–521, 1992
12. Pramming S, Thorsteinsson B, Bendtson I, Binder C: The relationship between symptomatic and biochemical hypoglycaemia in insulin-dependent diabetic patients. *J Intern Med* 228:641–646, 1990
13. 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 insulins obtained by protein engineering and their medical implications. *Nature* 333:679–682, 1988
14. Kang S, Creagh FM, Peters JR, Brange J, Vølund A, Owens DR: Comparison of subcutaneous soluble human insulin and insulin analogues (AspB9,GluB27; AspB10; AspB28) on meal related plasma glucose excursions in type I diabetic subjects. *Diabetes Care* 14:571–577, 1991
15. Heinemann L, Heise T, Jørgensen LN, Starke AAR: Action profile of the rapid acting insulin analogue: human insulin B28Asp. *Diabet Med* 10:535–539, 1993
16. Nielsen FS, Jørgensen 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
17. 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
18. Vignati L, Anderson J, Brunelle R: Efficacy of [Lys(B28),Pro(B29)] human insulin in a 1-year global randomized clinical trial (Abstract). *Diabetes* 42 (Suppl. 1):78A, 1994
19. Anderson JH, Brunelle RL, Koivisto VA, Pfützner A, Trautmann ME, Vignati L, DiMarchi R, the Multicenter Insulin Lispro Study Group: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 46:265–270, 1997
20. Anderson J, Symanowski S, Brunelle R: Safety of [Lys(B28),Pro(B29)] human insulin analog in long-term clinical trials (Abstract). *Diabetes* 43 (Suppl. 1):61A, 1994
21. Pfützner A, Küstner E, Forst T, Schulze-Schleppinghof B, Trautmann ME, Haslbeck M, Schatz H, Beyer J: Intensive insulin therapy with insulin lispro in patients with type I diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol* 104:25–30, 1996
22. Anderson JH, Brunelle RL, Arora V, Phillips JS, Vignati L, Koivisto VA, Trautmann ME: Effect of basal insulin on reduced frequency of nocturnal hypoglycemia in patients treated with insulin lispro (Abstract). *Diabetologia* 39 (Suppl. 1):A221, 1996
23. Pickup JC: Brittle diabetes. In *International Textbook of Diabetes Mellitus*. Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, Eds. John Wiley, New York, 1992, p. 1060
24. Pramming S, Thorsteinsson B, Bendtson I, Rønn B, Binder C: Nocturnal hypoglycaemia in patients receiving conventional treatment with insulin. *Br Med J* 291:376–379, 1985
25. Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vincenzo A, Epifano L, Ciofetta M, Pampanelli S, Brunetti P, Bolli GB: Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28),Pro(B29)] in IDDM. *Diabetologia* 37:713–720, 1994
26. Jacobs MAJM, Salobir B, Aarsen M, van Iperen A, Heine RJ: Hypoglycaemic thresholds for the glucose counterregulatory responses to Lys(B28)Pro(B29) human insulin analog. *Horm Metab Res* 26:A34, 1994
27. Tsui E, Chiasson JL, Tildesley H, Barnie A, Simkins S, Gao XJ, Zinman B: The use of insulin lispro in subcutaneous insulin pumps: counterregulatory hormone responses (Abstract). *Diabetologia* 39 (Suppl. 1):A223, 1996
28. Pramming S, Thorsteinsson B, Bendtson I, Binder C: Symptomatic hypoglycaemia in 411 type I diabetic patients. *Diabet Med* 8:217–222, 1991
29. Jørgensen 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
30. Zinman B, Tildesley H, Chiasson J-L, Tsui E, Strack T: Insulin lispro in CSII. *Diabetes* 46:440–443, 1997
31. Delahanty LM, Halford B: The role of diet behaviors in achieving improved glycemic control in intensively treated patients in the Diabetes Control and Complications Trial. *Diabetes Care* 16:1453–1458, 1993
32. Karşidag K, Satman I, Dinççag N, Altuntaş Y, Karadeniz Ş, Yilmaz MT: Comparison of metabolic control in IDDM with two different intensive regimens of [Lys(B28), Pro(B29)]-human insulin (lispro) plus NPH insulin (Abstract). *Diabetologia* 39 (Suppl. 1):A222, 1996
33. Torlone E, Pampanelli S, Lalli C, Del Sindaco P, Di Vincenzo A, Rambotti AM, Modarelli F, Epifano L, Kassi G, Perriello G, Brunetti P, 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
34. Talaulicar M, Willms B, Roβkamp R: Efficacy of HOE901 following subcutaneous injection for four days in type I diabetic subjects (Abstract). *Diabetologia* 37 (Suppl. 1):A169, 1994
35. Myers S, Yakubu-Madus F, Johnson W, Baker J, Cusick T, Williams V, Tinsley F, Kriauciunas A, Chen V: W99-S32: a soluble, basal insulin analog (Abstract). *Diabetologia* 38 (Suppl. 1):A4, 1995
36. Jonassen I, Havelund S, Kurtzhals P, Halstrom J, Ribel U, Hasselager E, Larsen UD, Markussen J: The potential therapeutic advantage of a novel, protracted, neutral soluble, albumin binding insulin analogue (Abstract). *Diabetologia* 38 (Suppl. 1):A4, 1995