Use of the Short-acting Insulin Analogue Lispro in Intensive Treatment of Type 1 Diabetes Mellitus: Importance of Appropriate Replacement of Basal Insulin and Time-interval Injection-meal

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To establish whether lispro may be a suitable short-acting insulin preparation for meals in intensive treatment of Type 1 diabetes mellitus (DM) in patients already in chronic good glycaemic control with conventional insulins, 69 patients on intensive therapy (4 daily s.c. insulin injections, soluble at each meal, NPH at bedtime, HbA_{1c} <7.5 %) were studied with an open, cross-over design for two periods of 3 months each (lispro or soluble). The % HbA_{1c} and frequency of hypoglycaemia were assessed under four different conditions (Groups I–IV). Lispro was always injected at mealtime, soluble 10–40 min prior to meals (with the exception of Group IV). Bedtime NPH was continued with both treatments. When lispro replaced soluble with no increase in number of daily NPH injections (Group I, $n = 15$), HbA_{1c} was no different (p = NS), but frequency of hypoglycaemia was greater ($p < 0.05$). When NPH was given 3–4 times daily, lispro (Group II, $n = 18$), but not soluble (Group III, $n = 12$) decreased HbA_{1c} by 0.35 ± 0.25 % with no increase in hypoglycaemia. When soluble was injected at mealtimes, HbA_{1c} increased by 0.18 ± 0.15% and hypoglycaemia was more frequent than when soluble was injected 10–40 min prior to meals (Group IV, $n = 24$) ($p < 0.05$). It is concluded that in intensive management of Type 1 DM, lispro is superior to soluble in terms of reduction of % HbA_{1c} and frequency of hypoglycaemia, especially for those patients who do not use a time interval between insulin injection and meal. However, these goals cannot be achieved without optimization of basal insulin.

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Introduction

The modern insulin therapy of Type 1 diabetes mellitus (DM) aims at maintaining chronic near-normoglycaemia to prevent the onset, or delay the progression of, microangiopathic complications.[1–5] Unfortunately, the peripheral, subcutaneous (s.c.) route of insulin administration is a poor surrogate of endogenous insulin secretion which occurs into the hepatic portal vein.[1] A serious obstacle to postprandial normoglycaemia in Type 1 DM is the slow absorption of short-acting insulin after s.c. injection, which results in hypoinsulinaemia 60–90 min after meals and inappropriate hyperinsulinaemia thereafter.[6,7] Consequently, postprandial hyperglycaemia and risk of hypoglycaemia later are common problems of patients with Type 1 diabetes mellitus.[6,7]

Short-acting insulin analogues are absorbed faster, produce greater peak in plasma, and ultimately result in less late hyperinsulinaemia after subcutaneous infection, compared to conventional soluble insulin.[8,9] Because of its pharmacokinetics and pharmacodynamics, the short-acting insulin analogue [Lys(B28), Pro(B29)], henceforth referred to as lispro (Eli Lilly & Co., Indianapolis, IN, USA),[8] improves the 2-h post-meal blood glucose and reduces the frequency of hypoglycaemia as compared to conventional soluble insulin.[10] However, in the several studies conducted so far with the short-acting insulin analogues in Type 1 DM, the long-term blood glucose control has not improved.[9–15] One possible explanation is that the shorter duration of action of lispro produces hypoinsulinaemia in the post-absorptive state.[16–18]

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Addition of basal insulin (NPH insulin) to the analogue dose to be injected at mealtime has been proposed as a possible remedy.[18,19] In fact, this is an alternative to the very successful replacement of basal insulin by continuous subcutaneous infusion, which does improve long-term blood glucose control when lispro is used.[20] To the best of our knowledge, no clinical trial has so far demonstrated that mealtime administration of lispro may result in better long-term blood glucose control as compared to conventional soluble insulin in Type 1 diabetes mellitus treated with multiple daily injections.

The present studies were undertaken to test the hypothesis that in Type 1 DM, mealtime s.c. injection of lispro improves long-term blood glucose control better than conventional soluble insulin, provided that at the same time basal insulin is replaced with multiple daily sc injections of NPH insulin.

Patients and Methods

Subjects

In order to minimize the effect of enrolment of Type 1 diabetes mellitus patients in a programme of intensive therapy *per se*, independent of lispro treatment, patients already established on long-term near-normoglycaemia, with glycosylated haemoglobin A_{1c} (HbA_{1c}) levels between 6.0 and 7.5%,[3] were studied. A total of 69 Type 1 diabetic patients were recruited among those attending the outpatient Diabetes Clinic of the Department of Internal Medicine and Endocrine and Metabolic Sciences (DiMISEM), University of Perugia (Table 1). These patients are being treated by our team with intensive insulin therapy and attend our Diabetes Clinic at least quarterly.[3] At the time of the study, all were C-peptide negative (plasma C-peptide <0.15 nmol l^{-1} 6 min after 1 mg glucagon i.v.). Patients were free of any detectable microangiopathic complication, and were negative at the screening for autonomic neuropathy, as judged on the basis of a standard battery of cardiovascular tests.[21] Institutional Review Board approval was obtained for these studies.

Design of Studies

During 1 month run-in period, patients continued their previously described model of insulin therapy,[3] i.e. soluble insulin (Humulin R, Eli Lilly & Co., Indianapolis, IN, USA) at breakfast, lunch and supper, and NPH insulin at bedtime. Thirty-four patients added NPH to soluble insulin at lunch (to a final ratio of ~30/70, NPH/soluble) to optimize pre-dinner blood glucose. Thereafter, patients were randomly assigned to four different groups, and studied for 6 months (each treatment for 3 months followed by cross-over) (Figure 1). The studies were open. Lispro was always injected immediately prior to meals (0–5 min), whereas conventional soluble insulin was injected 10–40 min prior to meals (with the exception of Group IV, see below) depending on pre-meal blood glucose concentration. Patients were instructed to aim for 90-min post-meal blood glucose between 9 and 10 mmol l^{-1} and for fasting and pre-meal blood glucose between 7 and 8 mmol l^{-1}.[3,22] NPH insulin was given according to different designs (see below), but the bedtime injection of NPH was continued with both treatments. In all studies, the 90-min postprandial blood glucose was used to titrate the dose of lispro or conventional soluble insulin, whereas the dose of daily

Table 1. Characteristics of patients with Type 1 diabetes mellitus at randomization

	Group I	Group II	Group III	Group IV
N	15	18	12	24
Age (yr)	33 ± 6.9	34 ± 7.2	32 ± 5.2	30 ± 8.8
Gender	7M, 8F	9M, 9F	6M, 6F	13M, 11F
BMI (kg/m^2)	22.1 ± 2.3	21.8 ± 1.6	23.0 ± 3.1	22.3 ± 2.4
Diabetes duration (yr)	15.2 ± 11.6	14.1 ± 8.9	13 ± 8.6	14 ± 10.2
HbA_{1c} (%)	6.43 ± 0.58	6.67 ± 0.4	6.35 ± 0.62	6.51 ± 0.58
Insulin treatment				
Daily injections	4	4	4	4
Total daily units	32 ± 7.7	33 ± 8	33 ± 7	34 ± 9.7
Daily units of short-acting	23 ± 3.8	20.1 ± 5.9	20 ± 2.8	23 ± 5.3
Daily units of NPH	13.2 ± 3.4	13 ± 4.2	12.2 ± 3.8	13.4 ± 5.8
Number of daily NPH insulin administrations	1.5 ± 0.5	1.5 ± 0.4	1.5 ± 0.7	1.4 ± 0.5
Frequency of hypoglycaemia[a]	5.7 ± 4.9	6.2 ± 4.7	6.5 ± 3.8	7.0 ± 2.9

[a]Episodes/patient-month blood glucose <3.3 mmol l^{-1}.

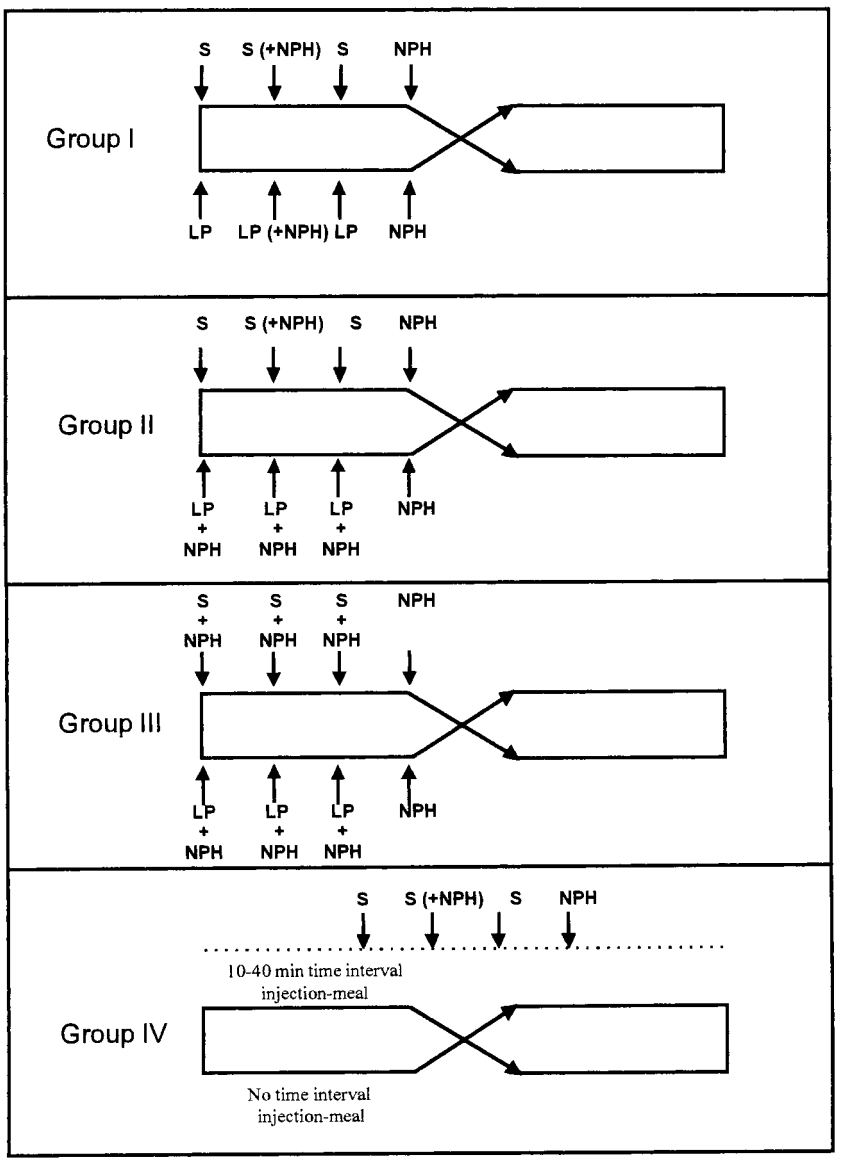

Figure 1. Design of the four (open), cross-over studies in patients with Type 1 diabetes mellitus. Each treatment was carried out for 3 months. In Group I, patients were treated either with conventional soluble insulin (S) given 10–40 min before meals or lispro (LP) at meals. NPH was continued in all patients at bedtime (and at lunch in some patients) with both treatments. In Group II, the conventional soluble insulin at meals of Group I was compared with a mixture of lispro and NPH at each meal. In Group III, the 4 times daily administration of NPH+lispro of Group II was compared with NPH+conventional soluble insulin at each meal. In Group IV, the effect of 10–40 min time interval between injection of conventional soluble insulin and meal, as compared to no interval, was assessed

and nocturnal NPH was based on fasting and pre-meal supper blood glucose values.

Group I ($n = 15$)

To test the effects of simple substitution of conventional soluble insulin with lispro on long-term blood glucose control, 8 patients continued their insulin treatment of the run-in period, whereas in the other 7 patients conventional soluble insulin was substituted with lispro for 3 months on a 'unit for unit' basis. During both treatments, the number of daily NPH injections was not changed but the dose of NPH was increased whenever needed in the attempt to maintain the desired glycaemic targets. After 3 months, the patients were crossed over to the other treatment for 3 additional months.

Group II ($n = 18$)

To test the effects of optimal replacement of basal insulin during lispro treatment at meals, 9 patients continued their treatment of the run-in period with conventional soluble insulin at meals, whereas the other 9 patients were given lispro at meals plus NPH at breakfast, lunch, and dinner whenever needed, for 3 months. The number of daily NPH injections (and dose) was increased whenever patients consistently observed fasting and/or pre-meal and bedtime blood glucose

concentrations greater than 9.0 mmol l^{-1} for more than 4 consecutive days. The percentage of NPH initially added to lispro was ~30 % of the total insulin dose at breakfast, ~40 % of the dose at lunch, and ~10 % of the dose at supper. These estimates were made based on previous experience with lispro + NPH mixtures as well as time interval between meals.[18,19] After, the patients were crossed over to the other treatment for 3 additional months.

Group III ($n = 12$)

To match patients of Group II on lispro and Humulin-R treatment for number of daily NPH insulin injections, and to prove that the beneficial effects on HbA_{1c} in Group II were specifically due to lispro rather than increased number of NPH injections, 6 patients received lispro + multiple NPH as in Group II, whereas the other 6 patients added NPH to conventional soluble insulin at breakfast, lunch, and dinner to a final ratio NPH/conventional soluble insulin superimposable to those of NPH/lispro of Group II, for 3 months. After this time, the patients were crossed over to the other treatment for 3 additional months.

Group IV ($n = 24$)

To test the effect of variable time interval between insulin injection and meal ingestion on long-term blood glucose control, 12 patients continued the run-in treatment with injection of conventional soluble insulin 10–40 min prior to meals depending on pre-meal blood glucose, whereas the other 12 patients always injected conventional soluble insulin 5 min prior to each meal irrespectively of pre-meal blood glucose, for 3 months. After this time, the patients were crossed over to the other treatment for 3 additional months. During both study periods patients maintained the same NPH treatment.

During run-in and treatment periods, patients were seen at 1–2 week intervals and were in frequent (even daily) telephone contact with us. At our centre, patients are offered a 24 h telephone service (mobile phone) for consultation.[3] All patients of Groups I and II and 18 patients from Groups III and IV mixed lispro or conventional soluble insulin with NPH before injection in syringes. The remaining patients used separate injections with pens to administer short- and intermediate-acting insulin. The diet of the run-in period was not changed during the treatment periods. Patients usually had three meals per day with no snacks.

In the run-in and both study periods, patients continued daily blood glucose monitoring prior to, and 90 min after, meals and at 03.00 h (the latter at least three times per week), measuring capillary blood glucose using chemistrips (Accutrend Glucose teststrips read by means of Accutrend Alpha reflectometer, Boehringer Mannheim, Germany). HbA_{1c} was measured at the end of the run-in, and the two treatment periods. To quantitate the frequency of hypoglycaemia, self-reported episodes were divided into severe (required assistance from a third party) and mild (self-treated episodes). The frequency of mild hypoglycaemia was estimated from patient's diary of blood glucose monitoring, and was divided into episodes with blood glucose between 3.3 and 2.8 mmol l^{-1}, between 2.8 and 2.2 mmol l^{-1}, or below 2.2 mmol l^{-1}.

Analytical Methods

HbA_{1c} was determined by a high performance liquid chromatography using a HI-Auto A1c TM HA 8121 apparatus (DIC, Kyoto Daiichi, Kogaku Co., Ltd., Japan) (range in non-diabetic subjects 3.8–5.5 %). The intra-assay coefficient of variation in the 5.0–8.0 % range in our laboratory is 1.2 %.

Statistical Methods

Data are mean ± SD in the text and Tables 1–3 and means ± SEM in Figures 2–6. The glucose values reported in the results are the means of all blood glucose determinations during the 3 month treatment. All analysis was carried out using a single value for each patient per cross-over period. Data were analysed by paired and, when appropriate, unpaired, *t*-test after analysis of variance for repeated measures. Briefly, order of treatments with two levels for each group (e.g. lispro–conventional soluble insulin and conventional soluble insulin–lispro) and time, with three levels (end of run-in, 3 month treatment and end of treatment) were included as independent variables. Blood glucose concentration, HbA_{1c} and daily dose were considered as dependent variables. A value of $p < 0.05$ was considered significant.[23]

Results

Frequency of Severe Hypoglycaemia and Body Weight

There were no episodes of severe hypoglycaemia. Body weight did not change in any of the groups studied (data not shown).

Group Studies I–IV

Group I: Effects of Substitution of Conventional Soluble with Lispro Insulin and no Change in Number of Daily NPH Insulin Injections

In these studies (Figures 2 and 3, Tables 2 and 3) lispro was used in place of conventional soluble on a unit-to-unit basis, while the dose but not the number of daily NPH insulin administrations was increased. Under these conditions, mean daily blood glucose concentration with lispro (8.8 ± 1.2 mmol l^{-1}) was similar to that with conventional soluble insulin (8.6 ± 0.8 mmol l^{-1}, p = NS). However, fasting, pre-meal and nocturnal blood glucose concentrations were greater with lispro than conventional soluble insulin (8.9 ± 1.1 vs 8.3 ± 1.2 mmol l^{-1}, $p < 0.05$). In contrast, 90

Table 2. Changes in the treatment strategy and outcome. In Group I patients, the number of daily NPH injections during lispro treatment was not increased as compared to run-in and conventional soluble insulin treatment. In contrast, in Group II patients given lispro, the number of NPH daily insulin injections was increased

	Group I		Group II	
	Lispro	Hum-R	Lispro	Hum-R
Daily insulin dose (Units)				
total	40 ± 0.7[b]	35 ± 9.4	32 ± 9.7	32.5 ± 9.7
short-acting	24.1 ± 6.2[b]	21.2 ± 4.6	13.8 ± 5.9[a]	19.2 ± 5.5
NPH	19.0 ± 7.0[b]	13.0 ± 3.5	17.4 ± 4.6[a]	12.9 ± 4.2
Insulin Units at injection times (short-acting/NPH)				
breakfast	5.5 ± 1.4[b]/none	4.9 ± 1.4/none	2.9 ± 1.2[a]/1.6 ± 0.8[a]	4.4 ± 1.6/none
lunch	8.9 ± 2.8[b]/3.1 ± 1.1[b]	7.8 ± 2.3/1.8 ± 1.4	5.4 ± 1.2[a]/3.7 ± 1.2[b]	7.4 ± 2.5/1.8 ± 1.6
supper	9.0 ± 2.3[b]/none	7.9 ± 1.9/none	5.9 ± 2.9[a]/0.6 ± 0.8[a]	7.7 ± 2.1/none
bedtime	none/16.1 ± 3.9[b]	none/11.3 ± 2.3	none/10.8 ± 2.5	none/10.6 ± 4.6
Number of insulin administrations day^{-1}				
NPH	1.5 ± 0.5	1.5 ± 0.5	3.8 ± 0.4[a]	1.5 ± 0.5
short-acting	3 ± 0	3 ± 0	3 ± 0	3 ± 0
Number of patients injecting NPH insulin day^{-1}				
Once (bedtime)	7	7	0	9
Twice (lunch and bedtime)	8	8	0	9
Three times	0	0	4	0
Four times	0	0	14	0

[a]$p < 0.005$ vs Hum-R; [b]$p < 0.05$ vs Hum-R.

Table 3. Frequency of hypoglycaemia (episodes/patients-month) in the four groups during the two treatments with lispro or conventional soluble insulin (Soluble) (see Method section). Episodes are calculated either as all episodes of blood glucose <3.3 mmol l^{-1} (total), or divided according to intervals of blood glucose

	Group I		Group II		Group III		Group IV	
	Lispro	Soluble	Lispro	Soluble	Lispro	Soluble	Soluble 10–40 min	Soluble 5 min
Blood glucose (mmol^{-1}l)								
3.3–2.8	3.2 ± 3.0[a]	2.6 ± 2.1	2.18 ± 1.6	1.93 ± 1.6	3.1 ± 2.4[a]	6.5 ± 4.1	2.8 ± 0.6[b]	4.1 ± 1.4
2.7–2.3	1.5 ± 1.1[a]	1.0 ± 0.7	0.99 ± 1.2	0.97 ± 0.8	1.4 ± 1.3[a]	3.4 ± 2.4	1.1 ± 0.4[b]	1.6 ± 0.9
<2.2	0.6 ± 0.7	0.4 ± 0.7	0.5 ± 0.8	0.5 ± 0.8	0.6 ± 0.3[a]	1.1 ± 0.7	0.5 ± 0.4[b]	1.1 ± 0.4
Total (blood glucose <3.3 mmol l^{-1})	5.3 ± 4.8	4.0 ± 3.4	3.65 ± 2.9	3.39 ± 2.9	4.4 ± 3.8[a]	11 ± 4.8	4.4 ± 1.4[b]	6.8 ± 2.4

[a]$p < 0.05$ vs Hum-R; [b]$p < 0.05$ vs Hum-R injected 5 min prior to meals as compared to 10–40 min before.

min post-meal blood glucose was lower with lispro as compared to Hum-R (8.9 ± 0.7 vs 9.2 ± 1.4 mmol l^{-1}, $p < 0.05$) (Figure 2). Lispro treatment was associated with a mean increase in the total insulin dose of 23 % due to both increase in short-acting insulin at meals of 15 % and NPH insulin of 44 % ($p < 0.05$ vs conventional soluble insulin) (Table 2). HbA_{1c} was no different after 3 month treatment with lispro and conventional soluble insulin (Figure 2). However, hypoglycaemia was more frequent with lispro than conventional soluble insulin (Table 3).

Group II: Effects of Substitution of Conventional Soluble with Lispro Insulin and Increase in Number of Daily NPH Insulin Injections

In these studies (Figures 3–5, Tables 2 and 3), lispro was used in place of conventional soluble insulin and combined with NPH at meals. Lispro treatment resulted in lower mean daily blood glucose as compared to conventional soluble insulin (8.1 ± 0.8 vs 8.6 ± 0.8 mmol l^{-1}, $p < 0.05$), associated with lower postprandial blood glucose (8.3 ± 0.7 vs 9.3 ± 0.8 mmol l^{-1}) ($p < 0.05$) and superimposable fasting,

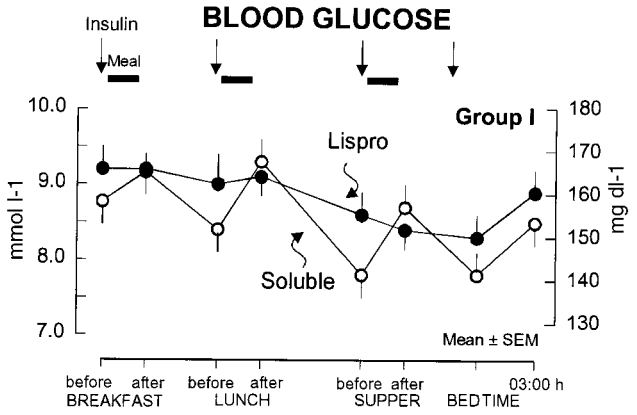

Figure 2. Blood glucose concentration (mean ± SEM, capillary blood, reflectometer chemistrip readings) during 3-month intensive therapy using either the short-acting insulin analogue lispro or conventional soluble insulin (Soluble) at meals in Group I patients with Type 1 diabetes mellitus. In this group, soluble insulin was simply substituted with lispro (no increase in the number of daily NPH injections)

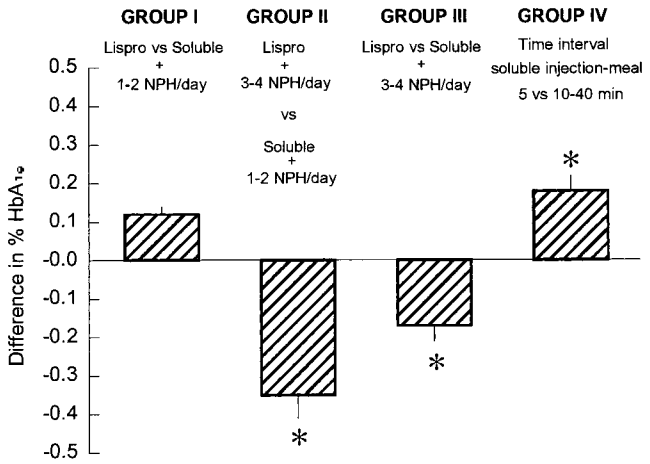

Figure 3. Differences in % HbA_{1c} (mean ± SEM) between the four treatment groups at the end of 3 months (see Methods and Figure 1) $p < 0.05$

pre-meal and nocturnal blood glucose concentrations (8.2 ± 0.7 vs 8.2 ± 0.7 mmol l^{-1}, lispro vs conventional soluble insulin, respectively, p = NS) (Figure 4). The total daily insulin dose during treatment with conventional soluble insulin and lispro + multiple NPH was no different. However, with the latter, 33 % more NPH and 27 % less short-acting insulin was needed (Table 2 and Figure 5). The % HbA_{1c} was lower after lispro + multiple NPH as compared to conventional soluble insulin by 0.35% (Figure 3), while the frequency of hypoglycaemia was similar (Table 3). These results were obtained by 14 patients injecting NPH four times daily, and 4 patients only three times daily (Table 2).

Group III: Effect of Treatment with Conventional Soluble Insulin and Multiple NPH Insulin Injections at Mealtime

These studies were designed to test the hypothesis that the improvement in HbA_{1c} observed in Group II was specifically due to lispro rather than multiple NPH injections

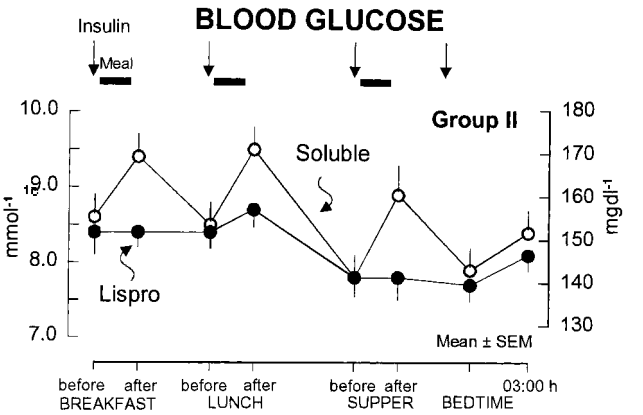

Figure 4. Blood glucose concentration (mean ± SEM, capillary blood, reflectometer chemistrip readings) during 3-month intensive therapy using either the short-acting insulin analogue lispro or conventional soluble insulin (Soluble) at meals in Group II patients with Type 1 diabetes mellitus. In this group, conventional soluble insulin was substituted with lispro combined with NPH at each meal (see Table 2)

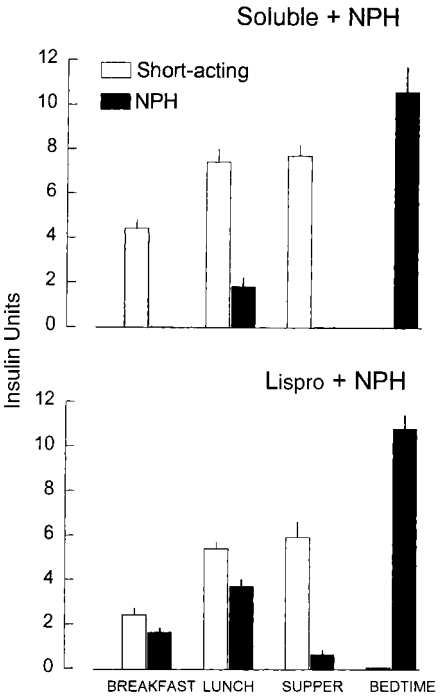

Figure 5. Mean insulin requirements of Type 1 diabetic patients of Group II (see Methods and Figure 1) during intensive treatment with conventional soluble or lispro insulin (mean ± SEM, data from Table 2)

at mealtime. Mean daily blood glucose concentrations remained lower when multiple NPH injections were given in combination with lispro (8.1 ± 0.8 mmol l^{-1}) as compared to conventional soluble insulin (8.5 ± 1.1 mmol l^{-1}, $p < 0.001$), as did the % HbA_{1c} (Figure 3). Insulin dose (total and ratio short-acting/NPH) was no different (p = NS, data not shown), but hypoglycaemia was more frequent when multiple NPH doses were combined with conventional soluble insulin (Table 3).

Group IV: Effect of Time Interval Between Injection of Conventional Soluble Insulin and Meal

When conventional soluble insulin was given 10–40 min prior to meals, mean blood glucose concentration (8.5 ± 1.1 vs 8.9 ± 1.2 mmol l^{-1}) (Figure 6), percentage of HbA_{1c} by 0.18 ± 0.15% (Figure 3), and frequency of hypoglycaemia (Table 3) were lower as compared to conventional soluble insulin given at mealtime ($p < 0.05$). There was no difference in the insulin dose (total, ratio soluble/NPH) between the two treatments (p = NS, data not shown).

Variability of BG Control

The variability of blood glucose was lower during treatment with lispro + multiple NPH as compared to conventional soluble insulin in Group II as compared to Group I, as indicated by the coefficients of variation of blood glucose (in mmol l^{-1}, calculated as mean ± SEM of coefficients of variations of daily blood glucose) (2.47 ± 0.5 vs 4.05 ± 1.0, $p < 0.05$).

Discussion

Despite clearcut evidence that lispro improves the 2-h post-meal blood glucose control in Type 1 DM, and contributes to reducing the frequency of hypoglycaemia, there are no studies proving its beneficial effects on overall glucose control in intensive management of Type 1 DM patients. Even a very recent review article[24] did not discuss indications for the use of lispro in intensive treatment of Type 1 DM. Because lispro improves the 2-h postprandial blood glucose, our question was how one could translate this advantage into a general improvement of 24-h blood glucose control, and possibly % HbA_{1c}, as compared to conventional soluble insulin.

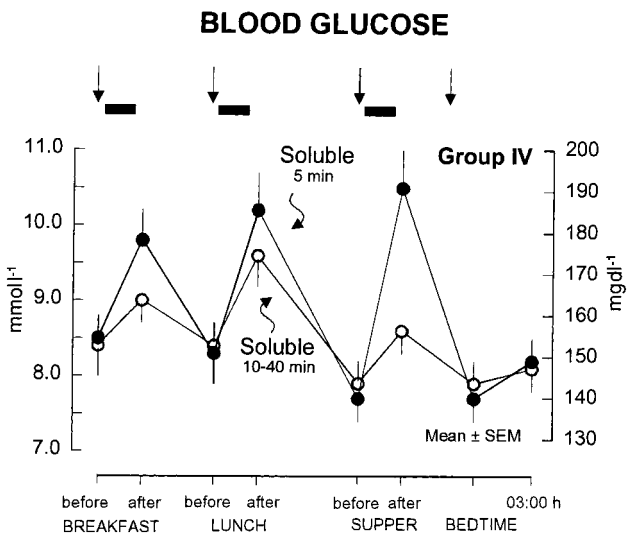

Figure 6. Blood glucose concentration (mean ± SEM, capillary blood, reflectometer chemistrip readings) during 3 month intensive therapy using conventional soluble insulin (Soluble) in Group IV patients with Type 1 diabetes mellitus. In this group, conventional soluble insulin was injected either at mealtime or 10–40 min prior to meal

Our results indicate first that lispro at meals improves long-term blood glucose only if basal insulin is optimally replaced by multiple daily NPH injections ; second that the improvement is specific for lispro and is not due to the extra NPH; third that improved control with lispro is not associated with greater frequency of hypoglycaemia; and fourth that the beneficial effects of lispro on % HbA_{1c} may be greater in those patients who usually do not use time interval between insulin injections and meals.

In these studies, substitution of conventional soluble insulin with lispro in the absence of changes in the strategy of use of basal insulin (Group I) did not improve long-term blood glucose despite lower 2-h post-meal blood glucose because of greater blood glucose in the post-absorptive state. At the same time, the risk for hypoglycaemia increased. This occurred despite an increase in NPH dose injected up to twice daily. Therefore, it is concluded that simple substitution of conventional soluble with lispro insulin at mealtimes may be more detrimental than beneficial for patients who are in optimal long-term blood glucose control with conventional soluble insulin,[3] if the number of NPH administrations is not increased at the same time. However, our data indicate that lispro at meals is advantageous when the strategy of replacement of basal insulin is also changed (as in our Group II). In these circumstances, not only is the 2-h postprandial blood glucose lower, but the fasting and pre-meal blood glucose is less than with conventional soluble insulin. HbA_{1c} decreases and the risk for hypoglycaemia is not increased. To the best of our knowledge, this is the first demonstration that lispro may be beneficial to long-term control of DM already in good control with conventional soluble insulin. These results help us to understand why, in previous studies in which replacement of basal insulin was not optimized, short-acting insulin analogues have not resulted in a decrease in HbA_{1c}.[9–15]

The strategy of multiple NPH doses used in the present studies in our Group II did not increase the frequency of hypoglycaemia, possibly because of the few NPH units added to each lispro administration. This helps in limiting the risk of hypoglycaemia unawareness.[3] That it was lispro and not the multiple daily NPH administrations that was responsible for the decrease in HbA_{1c} was proven in the present study in Group III by the failure of multiple daily NPH administration in combination with conventional soluble insulin to lower HbA_{1c}.

The modest decrement in HbA_{1c} (~0.4 %) in our Group II patients, comparable to the preliminary report from another study,[25] is estimated to decrease the risk of appearance and/or progression of microangiopathic complications by ~25 %.[4,26]

The effect of lispro + multiple NPH on HbA_{1c} we observed may be an underestimation of the potential of the strategy, because the comparable conventional sol-

uble insulin was given 10–40 min prior to each meal, as recommended.[6] However, a relatively high proportion of patients inject conventional soluble insulin and eat immediately.[27] Our data (from Group IV) show the potential importance of the injection–meal interval on diabetes control. For patients who usually inject conventional soluble insulin and eat immediately after, the benefits of lispro may be greater than shown.

The present study offers a practical example of successful transfer of patients already on long-term intensive therapy from conventional soluble insulin to lispro. Multiple daily NPH insulin administrations are recommended. With such a strategy, the requirements for the short-acting insulin (lispro) decrease by a percentage approximately similar to that of the increase in the NPH dose so there is no change of the total daily insulin dose. In the present studies, the ratio of lispro/NPH was ~65/35 at breakfast, ~60/40 at lunch, and ~10/90 at supper, and the majority of patients required NPH four times daily (Table 2). Of course these figures may be different in patients with different life-styles from those of the present studies and the timing of meals in this Italian population is relevant, as the dose of NPH added to lispro at meals was a function of the timeinterval between insulin injections. It is reasonable to assume this concept as a guideline in replacing basal insulin during lispro treatment at meals in Type 1 DM.

We observed less variability in blood glucose with lispro as compared to conventional soluble insulin. This is an anticipated but clinically relevant result because the faster the absorption from the subcutaneous tissue, the lower the size of the subcutaneous insulin depot, and the lower the variability of absorption.[28]

One might question whether lispro is a more suitable insulin preparation than conventional soluble insulin for intensive therapy of Type 1 DM in general. The present studies were performed in a group of Type 1 diabetic patients already trained to maintain good glycaemic control.[3] In this group, both lispro + multiple NPH and conventional soluble insulin + NPH treatments resulted in similarly optimal blood glucose control, as indicated by HbA_{1c},[3] and both regimens had a low frequency of hypoglycaemia. Lispro does offer some advantages to these patients. It helps improve life-style, because patients can inject and eat almost like non-diabetic subjects, while postprandial blood glucose control improves. This is perhaps the most important goal achieved with lispro, although difficult to quantitate and prove.[29] We were surprised by the acceptability of the complex insulin regimen of our Group II patients who injected NPH 3–4 times daily with lispro, which can be probably explained by the return of a more flexible lifestyle. Second, if basal insulin is optimally replaced (multiple NPH administrations or CSII), HbA_{1c} may decrease by ~0.4–0.6 %, the greatest improvement being anticipated in those patients who normally do not use a time interval between insulin injection and meal ingestion. Third, for a given value of % HbA_{1c} reached during intensive therapy, lispro may carry less risk of hypoglycaemia. Fourth, blood glucose values are less variable with lispro as compared to conventional soluble insulin.

However, in order to achieve these goals, it takes a good understanding of insulin strategies by the diabetologist, in continuing co-operation with motivated and educated patients. In particular, both the diabetologist and the patient who expect better long-term glycaemic control with lispro must be aware of the need for a better strategy of replacement of basal insulin. Failure to do so may ultimately result in worst control with lispro as compared to conventional soluble insulin.

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References

1. Shade S, Santiago JV, Skyler JS, Rizza RA, eds. *Intensive Insulin Therapy*. Amsterdam: Excerpta Medica, 1983.
2. Bolli GB. The pharmacokinetic basis of insulin therapy. *Diab Res Clin Prac* 1989; **6**: S3–S16.
3. Pampanelli S, Fanelli C, Lalli C, Ciofetta M, Del Sindaco P, Lepore M, *et al*. Long-term intensive insulin therapy: effects of HbA1c, risk for severe and mild hypoglycaemia, status of counterregulation and unawareness of hypoglycaemia. *Diabetologia* 1996; **39**: 677–686.
4. 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* 1993; **329**: 977–986.
5. Bolli GB. From physiology of glucose counterregulation to prevention of hypoglycaemia in Type 1 diabetes mellitus. *Diab Nutr Metab* 1990 ; **3**: 333–349.
6. Dimitriadis G, Gerich J. Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 1983; **6**: 374–377.
7. Pampanelli S, Torlone E, Lalli C, Del Sindaco P, Ciofetta M, Lepore M, *et al*. Improved postprandial metabolic control after subcutaneous injection of a short-acting insulin analogue in IDDM of short duration with residual pancreatic γ-cell function. *Diabetes Care* 1995; **18**: 1452–1459.
8. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)] human insulin. A rapidly absorbed analogue of human insulin. *Diabetes* 1994; **43**: 396–402.
9. 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* 1995; **38**: 592–598.
10. Anderson JH, Brunelle R, Koivisto VA, Pfuetzner A, Trautman M, Vignati L, *et al*. Insulin analogue treatment reduces postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients. *Diabetes* 1997; **46**: 265–270.

11. Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK, *et al*. Pre-meal insulin analogue insulin lispro vs Humulin R insulin treatment in young subjects with Type 1 diabetes. *Diabetic Med* 1996; **13**: 47–52.
12. Pfuetzner A, Kuestner E, Forst T, Schulze-Schleppinghoff B, Tratuman M, Haslbeck M, *et al*. Intensive insulin therapy with insulin lispro in patients with Type 1 diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol* 1996; **104**: 25–30.
13. Rowe R, Anderson JH, Gale E. A double-blind comparison of insulin Lispro and regular insulin in patients on a multiple injection regimen. *Diabetes* 1996; **45** (suppl 2): 71A.
14. Jacobs MAJM, Keulen ETP, Kanc K, Casteleijn S, Scheffer P, Deville W, *et al*. Metabolic efficacy of preprandial administration of Lys(B28),Pro(B29) human insulin analog in IDDM patients. *Diabetes Care* 1997; **20**: 1279–1286.
15. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson J, *et al*. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care* 1997; **20**: 1827–1832.
16. Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, Di Vincenzo A, *et al*. Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28),Pro(B29)] in IDDM. *Diabetologia* 1994; **37**: 713–720.
17. Tuominen JA, Karonen S-L, Melamies L, Bolli G, Koivisto VA. Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue. *Diabetologia* 1995; **38**: 106–111.
18. Torlone E, Pampanelli S, Lalli C, Del Sindaco P, Di Vincenzo A, Rambotti AM, *et al*. Effect of the short-acting insulin analog [Lys(B28),Pro(B29)] on postprandial blood glucose control in IDDM. *Diabetes Care* 1996; **19**: 945–952.
19. Ebeling P, Jansson P-A, Smith U, Lalli C, Bolli GB, Koivisto VA. Strategies towards improved control during insulin lispro therapy : importance of basal insulin. *Diabetes Care* 1997; **20**: 1287–1289.
20. Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack TR. Insulin Lispro in CSII: results of a double-blind crossover study. *Diabetes* 1997; **46**: 440–443.
21. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982; **285**: 916–918.
22. Bolli GB, Perriello G, Fanelli C, De Feo. Nocturnal blood glucose control in Type 1 diabetes mellitus. *Diabetes Care* 1993; **16** (suppl 3): 71–89.
23. Zar J. *Biostatistical Analysis*. Englewood Cliffs: Prentice Hall, 1984.
24. Holleman F, Hoekstra JBL. Insulin lispro. *N Engl J Med* 1997; **337**: 176–183.
25. Ebeling P, Jansson P-A, Smith U, Conget I, Coves MJ, Gomis R, *et al*. Optimal combination of insulin lispro and basal insulin improves glycemic control in IDDM. *Diabetologia* 1997; **40** (suppl 1): A351.
26. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 1995; **44**: 968–983.
27. Lean MEJ, Ng LL, Tennison BR. Interval between insulin injection and eating in relation to blood glucose control in adult diabetics. *Br Med J* 1985; **290**: 105–108.
28. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. *Diabetes Care* 1984; **3**: 188–199.
29. Rosenberg WM, Sackett DL. On the need for evidence-based medicine. *Therapie* 1996; **51**: 212–217.