Meta-Analysis of the Effect of Insulin Lispro on Severe Hypoglycemia in Patients With Type 1 Diabetes

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OBJECTIVE — A precise time-action profile of insulin lispro (Humalog) at mealtime may reduce the incidence of severe hypoglycemia. Because it is a rare complication, we performed a cumulative meta-analysis to compare the frequency of severe hypoglycemia during insulin lispro and human regular insulin therapy in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — The analysis included eight large multicenter clinical trials, three with parallel and five with crossover designs. The studies included 2,576 type 1 diabetic patients in total, with 2,327 receiving insulin lispro and 2,339 receiving regular human insulin, representing >1,400 patient-years of insulin therapy. Severe hypoglycemia was defined as coma or requiring glucagon or intravenous glucose. The patients received either NPH or ultralente as their basal insulin and insulin lispro or regular human insulin before each meal.

RESULTS — Seventy-two patients (3.1%) had a total of 102 severe hypoglycemic episodes during insulin lispro therapy, compared with 102 patients (4.4%) with a total of 131 episodes during regular human insulin therapy ($P = 0.024$).

CONCLUSIONS — The results of this meta-analysis demonstrate that in type 1 diabetic patients, the frequency of severe hypoglycemia can be reduced by taking insulin lispro as compared with regular human insulin therapy.

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Intensive insulin treatment and improved glycemic control is demonstrated to reduce the risk of development and progression of microvascular and neurological long-term complications in type 1 diabetic patients (1,2). Intensive therapy therefore should be indicated in most type 1 diabetic patients with the goal of maintaining blood glucose and HbA_{1c} levels as close to normal as possible without compromising patient safety (2,3).

Hypoglycemia is the most common adverse effect of intensive insulin therapy, and severe hypoglycemia is the most feared complication of insulin therapy (4). Although the increase in severe hypoglycemia with the intensification of therapy is not a universal finding (5,6), in some studies the proportion of patients experiencing severe hypoglycemic episodes has increased during intensive therapy. During a 6.5-year follow-up in the Diabetes Control and Complications Trial (DCCT), 35% of patients in the conventional treatment group and 65% in the intensive group had at least one episode of severe hypoglycemia (7). In the Stockholm Diabetes Intervention Study, the corresponding figures were 73% and 86% during a 10-year follow-up period (8). In a recent meta-analysis, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventional and intensively treated patients, respectively (9). The odds ratio for severe hypoglycemia was 2.99 during intensified insulin therapy as compared with conventional treatment (9). Severe hypoglycemia can be associated with significant morbidity, including death (4), and recurrent severe hypoglycemia may lead to cumulative cognitive impairment (10).

Insulin lispro (Humalog) is a rapid-acting analog of human insulin that is absorbed more rapidly than regular human insulin from subcutaneous injection sites. This results in a faster onset of action, a shorter time to peak activity, and a shorter duration of action compared with regular human insulin (11). This activity profile decreases the postprandial rise in blood glucose both in type 1 (11–13) and in type 2 diabetic patients (14,15), when compared with equivalent dosages of regular human insulin. Studies with insulin lispro have reported reduction in the frequency of symptomatic and biochemical hypoglycemia (12–14) and in the frequency of nocturnal hypoglycemia (12,16).

The incidence of severe hypoglycemia defined as a coma or requirement of glucagon or intravenous glucose is small, and none of the individual clinical trials has been powered to detect a significant difference in this outcome between insulin lispro and regular human insulin. Consequently, in the present study, we combined the data from all the large clinical trials currently available in type 1 diabetic patients and performed a meta-analysis to compare the frequency of severe hypoglycemic episodes during insulin lispro and regular human insulin therapy.

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Abbreviations: DCCT, Diabetes Control and Complications Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Summary of studies used in this meta-analysis*

Study	Design	Duration	Patient and study characteristics	Basal insulin	Number of patients		Reference
					Lispro	Soluble	
1	Parallel	1 year	Adult	NPH	81	86	15
2	Parallel	1 year	Adult	UL	81	88	15
3	Parallel	1 year	Adult/newly diagnosed	NPH/UL	50	48	Unpublished
4	Crossover	6 months	Adult	NPH/UL	990	995	12
5	Crossover	4 months	Adult/twice-daily injection	NPH	375	89	47
6	Crossover	6 months	Adult/double-blind	NPH	92	377	48
7	Crossover	6 months	Adult/Actrapid as control*	NPH	198	194*	39
8	Crossover	8 months	Adolescents	NPH	460	462	49
Total					2,327	2,339	

All studies used intensive therapy with the exception of study 5. *Actrapid as premeal insulin. UL, ultralente.

RESEARCH DESIGN AND METHODS

— We identified in the database of Eli Lilly, the manufacturer of insulin lispro, eight large randomized clinical trials comparing insulin lispro with regular human insulin, either Humulin Regular (Eli Lilly, Indianapolis, IN) or Actrapid (Novo Nordisk, Copenhagen). All of these trials were included in this meta-analysis (Table 1). These studies include 2,576 type 1 diabetic patients in total, of whom 2,327 were treated with insulin lispro. The studies represent all of the large clinical trials in patients with type 1 diabetic patients using insulin lispro that have been performed to date. None of these studies were powered to detect a significant difference in severe hypoglycemia using the strict criteria of the present study. We excluded acute pharmacokinetic trials (17–26), case reports (27–29), and smaller studies with different objectives or the lack of a control group treated with human soluble insulin (30–33). The total of 233 patients from these small studies was not included in this meta-analysis. Each of the included studies was a multicenter trial and involved investigators from various countries, including the U.S., Canada, several European and Mid-Eastern countries, South Africa, Australia, and New Zealand. The primary objectives of these studies were to compare insulin lispro and regular human insulin with respect to postprandial glucose level, frequency of hypoglycemic episodes, metabolic control, and safety in patients with type 1 diabetes. A history of recurrent severe hypoglycemia was an exclusion criterion in these studies. Study quality assessment was made by reviewing the designs and implementation of each study. Each of the eight studies had a formal protocol and used standardized case report forms. The case report forms and the methods for the collection and storage of the clinical trial data were similar in all studies. The investigators and study coordinators were trained similarly, and the collection and the quality of the data were reviewed in a consistent fashion. The study characteristics were carefully evaluated and are presented in Table 1. These include the study design, type of treatment and control, sample size, and the date the study was completed. The study outcomes were obtained, and a consistent definition for severe hypoglycemia (coma or requiring glucagon or intravenous glucose) was used to obtain the frequency and incidence in each study because all the hypoglycemia data were available. All the data from these studies were available for this meta-analysis. Data from individual patients were merged into a master database on which subsequent analyses were based.

The patients in these studies received either NPH or ultralente (Eli Lilly, Indianapolis, IN) as their basal insulin. They were instructed to inject a dose of rapid-acting insulin—insulin lispro or human soluble insulin—into the subcutaneous tissue of the abdomen before each meal (any consumption of food that contained >20% of their total daily caloric intake, with the exception of study 5 [47]). In seven of eight studies, patients were advised to inject insulin lispro ≤15 min before the meal and the regular human insulin 30–45 min before the meal. One study (8) had a double-blind design and the patients administered both types of insulin ≤15 min before a meal. Insulin doses and dietary instructions were adjusted based on glucose self-monitoring and the metabolic needs of the patient. Glycemic targets were fasting blood glucose values <7.8 mmol/l without hypoglycemia and maintenance of 2-h postprandial glucose values <10 mmol/l.

Patients were asked to answer a standard battery of seven questions intended to characterize the severity and nature of each hypoglycemic episode. Included in this standardized questionnaire were questions concerning the use of glucagon and intravenous glucose as treatment for the hypoglycemic event, and whether it resulted in coma. In this meta-analysis, a severe hypoglycemic episode was defined as an episode resulting in a coma or requiring glucagon or intravenous glucose. This definition was used to evaluate each of the hypoglycemic episodes reported in these studies.

Statistical analysis

The technique for performing a meta-analysis in a cumulative process was used as described by Lau et al. (34). These studies were arranged in chronological sequence by study completion. A Cochran-Mantel-Haenszel test was used to compare the treatment groups for the incidence of severe hypoglycemic events. This technique, which takes into account the possible heterogeneity between individual studies, is commonly used in combining incidence results from meta-analysis (35–37). A sensitivity analysis was performed to examine the effects of the various studies on the overall outcome. This was accomplished by performing a cumulative meta-analysis in chronological order on completion of each of the individual studies (34). A χ^2 test was also used to compare the number of patients experiencing at least one severe hypoglycemic event between the two study groups for each of the individual studies.

To perform this meta-analysis, the data from parallel and crossover studies had to be

Table 2—*Number of severe hypoglycemic episodes and frequency (%) of patients with at least one severe hypoglycemic episode by study*

	Lispro			Soluble			
Study	Episodes	Frequency	%	Episodes	Frequency	%	*P* value
1	15	5/81	6.2	7	7/86	8.1	0.623
2	12	9/81	11.1	16	8/88	9.1	0.663
3	1	1/50	2.0	1	1/48	2.1	0.977
4	30	24/990	2.4	42	36/995	3.6	0.120
5	17	11/375	2.9	13	12/377	3.2	0.842
6	3	2/92	2.2	10	6/89	6.7	0.135
7	8	7/198	3.5	18	14/194	7.2	0.106
8	16	13/460	2.8	24	18/462	3.9	0.367
All studies	102	72/2,327	3.1	131	102/2,339	4.4	0.024

P values were calculated by χ^2 test for the individual studies and a Cochran-Mantel-Haenszel test for the analysis combining all of the studies.

combined. The patients within the crossover studies received both insulin lispro and regular human insulin. These crossover data were split to make the crossover data look like a parallel study and thus represent patient exposures. This technique removes the natural pairing of the treatments within a patient and thus tends to reduce the ability of showing a treatment difference even though the sample size is increased. An additional analysis examining the results from the crossover studies only was performed to evaluate these results separately from the parallel studies. This analysis was performed using a McNemar's test, which takes into account the paired categorical measurements. The results were consistent when the data were combined with the data from parallel studies, thus demonstrating the validity of combining the crossover data with the parallel data. The number of severe hypoglycemic episodes per 100 patient-years was computed by dividing the number of severe hypoglycemic episodes by the years of exposure and then multiplying by 100. The analyses were performed using the statistical package SAS (38).

RESULTS — The numbers of severe hypoglycemic episodes, frequency, and percent of patients who experienced at least one episode of severe hypoglycemia in each individual study are shown in Table 2. In no instance was there a statistically significant difference between the treatments for the incidence of severe hypoglycemic events within the individual studies. Combining all eight studies, 2,327 patients received insulin lispro and 2,339 patients received regular human insulin therapy. Within these studies, 72 patients had a total of 102 severe hypoglycemic episodes during insulin lispro therapy compared with 102 patients with a total of 131 episodes during regular human insulin therapy ($P = 0.024$). There was no significant difference in the diurnal distribution of severe hypoglycemia between the two therapies. The proportion of severe hypoglycemic episodes between midnight and 6:00 A.M. was 31% during insulin lispro and 34% during regular human insulin therapy. The rate of severe hypoglycemia per 100 patient-years was 14.2 during insulin lispro and 18.2 during regular human insulin therapy.

The results of the cumulative meta-analysis in Table 3 are sorted by the time of the individual study completion date. The initial three parallel studies were completed before the crossover studies. The results from the cumulative analysis are presented as ratio of therapies for the percent of patients experiencing at least one severe hypoglycemic episode (lispro/regular insulin). This method also adjusts for the differing study lengths. Figure 1 illustrates this cumulative effect of the difference between the treatment groups. As the studies are accumulated, the 95% CI becomes narrower and demonstrates that the incidence of severe hypoglycemic episodes is lower during insulin lispro therapy. The cumulative relative risk approaches 0.7 when all of the clinical trials are combined (Table 3). There was thus a 30% overall decrease in the risk of a patient having a severe hypoglycemic episode during insulin lispro therapy compared with regular human insulin treatment.

Because in the crossover studies each patient received both therapies, these studies provide an opportunity for paired analysis of severe hypoglycemia. Within the crossover studies alone, the number of patients with at least one severe hypoglycemic episode during insulin lispro therapy was lower than the number during regular human insulin therapy ($P = 0.019$, Table 4). This paired analysis is consistent with the results of the cumulative meta-analysis that combines all of the study results.

To analyze whether the difference in severe hypoglycemia rate was related to difference in glycemic control, a meta-analysis of HbA_{1c} was performed in all eight studies. The HbA_{1c} values were virtually identical at the end point during insulin lispro (8.15 ± 1.50%, mean ± SD) and during regular human insulin therapy (8.14 ± 1.52%, $P = 0.370$).

CONCLUSIONS — The severity of hypoglycemia is conventionally graded according to the need for assistance from another person, as in the DCCT (2, 8). Using this definition, 3,788 episodes of severe hypoglycemia occurred in the course of the DCCT, with 1,027 associated with coma or seizure. The event rate per 100 patient-years for severe hypoglycemia defined as coma or

Table 3—*Cumulative meta-analysis of frequency of severe hypoglycemia by order of study completion*

Study	Lispro (%)	Soluble (%)	Relative risk	*P* value	95% CI
1	5/81 (6.2)	7/86 (8.1)	0.742	0.624	0.226–2.441
1–2	14/162 (8.6)	15/174 (8.6)	1.005	0.990	0.468–2.157
1–3	15/212 (7.1)	16/222 (7.2)	1.002	0.997	0.479–2.094
1–4	39/1,202 (3.2)	52/1,217 (4.3)	0.760	0.204	0.497–1.161
1–5	50/1,577 (3.2)	64/1,594 (4.0)	0.790	0.222	0.542–1.153
1–6	52/1,669 (3.1)	70/1,683 (4.2)	0.747	0.118	0.518–1.077
1–7	59/1,867 (3.2)	84/1,877 (4.5)	0.700	0.039	0.499–0.982
1–8 (All)	72/2,327 (3.1)	102/2,339 (4.4)	0.703	0.024	0.518–0.956

P values for meta-analyses were calculated using Cochran-Mantel-Haenszel test.

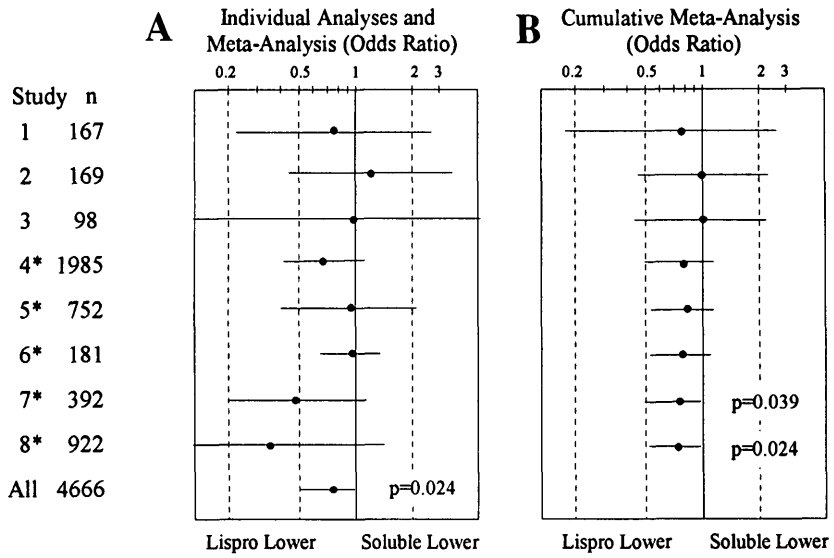

Figure 1—*Individual analyses (A) and cumulative meta-analysis (B) of clinical trials examining the incidence of severe hypoglycemic episodes during insulin lispro and soluble human insulin therapy. The odds ratios and 95% CIs for the effect of insulin lispro on the reduction of the incidence of severe hypoglycemic episodes are shown on a logarithmic scale.*

seizure was 5.4 in the conventional treatment group and 16.3 in the intensive treatment group (8). Severe hypoglycemia, however defined, may therefore be considered unacceptably frequent even on conventional therapy; and there is a clearly increased risk in some (7–9) although not all studies (5,6) when intensified therapy is introduced. Any form of therapy with the potential to reduce the risk of severe hypoglycemia therefore deserves serious scrutiny.

For purposes of the present analysis we chose a more rigorous definition of severe hypoglycemia, as resulting in coma and/or requiring intravenous glucose or intramuscular glucagon. This differs to some extent from the DCCT definition as coma and/or seizure, but in the current study, the frequency per 100 patient-years (14.2 in the lispro group and 18.2 in the regular human insulin group) was similar to that reported for patients on DCCT intensive therapy (16.3). The stricter definition was selected for the meta-analysis because it represents an objective end point that we would expect to be recorded in a consistent manner by local investigators participating in the large series of multinational studies summarized in this report. The consequence of adopting this more limited definition of severe hypoglycemia is that the number of episodes available is restricted. In total, 174 patients were affected on 233 occasions in these trials, from a total of 4,666 patient exposures to either insulin lispro or regular human insulin. The eight studies making up the meta-analysis individually lacked the power to detect a significant difference when the current strict criteria for severe hypoglycemia were used. When criteria included inability to treat oneself, in one individual trial the total number of hypoglycemic events was 94 in 199 patients, with significantly fewer episodes during insulin lispro than during regular human insulin therapy (study 7 [39]). When stricter criteria and a more conservative statistical approach were used, the difference was no more statistically significant in the current analysis (Table 4, Fig. 1). Because of the clinical importance of severe hypoglycemia, a meta-analysis with rigorous definition of severe hypoglycemia and a conservative statistical analysis is appropriate in this situation. When the strict criteria of severe hypoglycemia and a conservative statistical analysis are used as in the current study, a meta-analysis of a large patient population rather than data from smaller studies would reveal any differences in a rare event such as severe hypoglycemia.

A meta-analysis entails the application of uniform methods in the planning, data collection, analysis, and reporting of the results from various clinical trials into a single analysis (34–37). A meta-analysis should contain a specific hypothesis of interest and develop inclusion/exclusion criteria for all possible studies, study quality assessment, study characteristics and outcomes, pooling procedures, and sensitivity analyses. This meta-analysis was performed to meet all these criteria. The hypothesis was to estimate the incidence of severe hypoglycemia during insulin lispro therapy and to compare this incidence to that during soluble human insulin. Because this is a relatively new insulin, the existence of all large, randomized clinical trials using insulin lispro were well documented, even if the results had not been published. Studies were selected according to the following criteria: completed in type 1 diabetic patients, measured hypoglycemia using a standard hypoglycemia questionnaire, enrolled at least 50 patients, were randomized, and were at least 2 months in duration. Eight studies were found that met this criteria.

Certain preconditions need to be fulfilled before a meta-analysis can be considered appropriate. These include a clear definition of the end point, which is the case in the present study. The studies were performed in a closely comparable fashion; the same definition of severe hypoglycemia

Table 4—*Analysis of the crossover studies taking into account the paired responses*

Study	Frequency of patients with a severe hypoglycemic episode				*P* value
	−L −S	+L +S	+L −S	−L +S	
4	927	7	17	26	0.222
5	353	3	8	9	1.000
6	82	1	1	4	0.371
7	174	2	5	12	0.146
8	431	4	9	14	0.404
Total	1,967	17	40	65	0.019

P values were calculated using McNemar's test for paired observations. −L −S, number of patients without a severe hypoglycemic episode during either insulin lispro (L) or soluble insulin (S) therapy; +L +S, number of patients with at least one severe hypoglycemic episode during both L and S therapy; −L +S, number of patients with at least one severe hypoglycemic episode during only S therapy; and +L −S, number of patients with at least one severe hypoglycemic episode during only L therapy.

was applied consistently throughout; and a rigorous definition of end point was chosen to minimize possible variation in reporting by local clinicians. All relevant studies have been included, which is to say all major studies to date comparing insulin lispro with soluble insulin in patients with type 1 diabetes. A number of smaller studies with more varied protocols and objectives have not, however, been included in the analysis. In general, the consistency between the protocols has resulted in creation of a database in which the individual studies are highly comparable. The conditions for undertaking a meta-analysis were therefore satisfied in the current study.

Meta-analysis has been recently criticized because of discrepancies between the results of meta-analysis and subsequent large randomized trials (40–42). Our meta-analysis included >90% of the type 1 diabetic patients using insulin lispro therapy published so far. In addition, our meta-analysis includes all large trials, whereas the discrepancy is observed when results of meta-analyses that include a number of small trials are compared with large individual studies (40). Thus, it is very unlikely that there will be a discrepancy between our meta-analysis and possible later clinical trials. If there are further trials with insulin lispro, any individual study will probably not have enough statistical power to demonstrate significant treatment differences in the rate of severe hypoglycemia because of its rare occurrence.

The meta-analysis revealed a significant reduction in severe hypoglycemia during lispro therapy. Although the difference in the absolute number (102 vs. 131) or frequency (3.1 vs. 4.4%) of episodes was quite small, considering the severe nature of this complication, the reduction is also clinically significant. The reduction was not due to a difference in overall glycemic control, because HbA_{1c} levels were similar in the two treatment groups. The difference could, at least in part, be accounted for by a more precise time action profile at mealtimes of insulin lispro and lesser overlapping with basal insulin due to a shorter duration of action with insulin lispro compared with regular human insulin. It should be noted that patients with a history of recurrent severe hypoglycemia were excluded from the trials included here. Therefore, the risks reported here may underrepresent the general population of type 1 diabetic patients.

The observation that insulin lispro can reduce the incidence of severe hypoglycemia may have a number of clinical implications. First, risks during intensive insulin therapy will be reduced, thus facilitating the aim of achieving better glycemic control to reduce long-term complications. Second, reduction of hypoglycemia can restore the counterregulatory response to hypoglycemia and improve hypoglycemia awareness among type 1 diabetic patients (43). Third, both somatic morbidity and psychological anxiety (44,45) associated with hypoglycemia can be reduced. A smaller risk of severe hypoglycemia should help to improve the quality of life, compliance with insulin therapy (46), and long-term prognosis of patients with type 1 diabetes.

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