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Basal-bolus insulin therapy in Type 1 diabetes: comparative study of pre-meal administration of a fixed mixture of insulin lispro (50%) and neutral protamine lispro (50%) with human soluble insulin

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Abstract

Aims To ascertain whether pre-meal administration of 50% insulin lispro and 50% neutral protamine lispro (NPL), given as a fixed mixture (Humalog® Mix50™, Eli Lilly) (Mix50), provides satisfactory glycaemic control throughout the day compared with pre-meal human soluble (regular) insulin as a basal-bolus regimen in people with Type 1 diabetes. Both regimens included bedtime human isophane (NPH) insulin.

Methods This was a multinational, multicentre, randomized, open-label, two-period crossover comparison of two insulin treatments for two 12-week periods in 109 patients with Type 1 diabetes. The protocol provided preliminary evaluations of dose requirements and recommendations for insulin dose adjustment when switching regimens on the basis of blood glucose (BG) values. Eight-point BG profiles, frequency of hypoglycaemia, HbA_{1c}, insulin dose, time of injection, and frequency of snacking were assessed during each treatment.

Results Total daily insulin dose was similar for both treatments, but the total pre-meal doses were higher ($P < 0.001$) and the bedtime dose of isophane was lower ($P < 0.001$) with Mix50. The pre-meal dose before breakfast and lunch, although statistically different ($P = 0.006$ and $P < 0.001$, respectively), was of similar magnitude, but the pre-evening meal dose was higher with Mix50 ($P < 0.001$). Median (interquartile range) time of insulin injection before meals was: Mix50 4.2 (25th percentile = 1.0; 75th percentile = 6.3) min, human soluble insulin 24.6 (25th percentile = 16.6; 75th percentile = 30.0) min. Pre-meal and bedtime BG concentrations did not differ between treatments. The BG 2 h after the evening meal was lower with Mix50 (8.40 ± 2.95 mmol/l vs. 9.60 ± 3.47 mmol/l) ($P = 0.049$). BG after breakfast and lunch, mean HbA_{1c}, frequency of hypoglycaemia, frequency of snacks, and body weight were not different.

Conclusion The use of Mix50 in a basal-bolus regimen achieved similar control of pre-meal BG to human soluble insulin, and overall glycaemic control and hypoglycaemia risk were equivalent. This suggests that Mix50 can provide an adequate supply of insulin to control BG between meals while providing the convenience of injecting immediately before meals.

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Keywords Type 1 diabetes, fixed insulin lispro mixtures, hypoglycaemia, insulin analogue

Abbreviations diabetes, diabetes mellitus; NPH, neutral protamine Hagedorn; NPL, neutral protamine lispro; HbA_{1c}, haemoglobin A_{1c}; NS, not significant; SD, standard deviation

Introduction

In the management of Type 1 diabetes, a basal-bolus insulin regimen attempts to simulate the normal physiological secretory pattern of insulin in response to food by injecting a short-acting, soluble (regular) insulin before meals and an intermediate-acting insulin (usually isophane [NPH]) at bedtime, or more frequently if necessary [1]. Basal-bolus insulin regimens allow greater flexibility in the timing of meals than twice daily administration of soluble and basal insulins given in combination, and may reduce the need for snacks between meals. The use of the newer rapid-acting insulin analogues, insulin lispro (Humalog®; Eli Lilly and Company) and insulin aspart (Novorapid™; Novo Nordisk), has increased convenience of administration as they can be injected immediately before, during, or after meals [2,3], avoiding the need for a premeditated interval between the injection of insulin and ingestion of food [4].

However, the short duration of action of rapid-acting insulin analogues leads to waning of insulin activity between meals, allowing blood glucose to rise before the next meal [5]. This may be a particular problem when there is a long period between meals and administration of insulin. While the longer duration of action of soluble insulin minimizes this effect, this is offset by a greater risk of inducing late post-prandial hypoglycaemia. To avoid a potential deterioration of glycaemic control between meals with pre-meal insulin analogues, the administration of additional isophane insulin before breakfast has been utilized. Alternatively, a mixture of short and intermediate-acting insulins may be administered before all major meals and supplemented by basal insulin given alone at bedtime. The use of these regimens in people with Type 1 diabetes can improve overall glycaemic control with no increased risk of hypoglycaemia [6,7].

Premixed insulin preparations (fixed mixtures) of insulin lispro and an intermediate-acting insulin (a crystalline suspension of neutral protamine lispro, known as NPL) are available commercially. Humalog® Mix 50™ (Mix50) consists of 50% insulin lispro and 50% NPL. In a small pilot study of eight subjects with Type 1 diabetes, a fixed mixture of 30% human soluble insulin and 70% human isophane insulin (Humulin® M3, Eli Lilly) was compared with different fixed mixtures of insulin lispro and NPL (25% lispro and 75% NPL [Humalog® Mix25™]; Mix50). The insulin lispro mixtures achieved a similar quality of glycaemic control with fewer reported episodes of hypoglycaemia [8]. Another study [9] compared the administration of a fixed mixture of 50% insulin lispro and 50% NPL before breakfast and a fixed mixture of 25% insulin lispro and 75% NPL before the evening meal with a fixed mixture of 50% human soluble insulin and 50% human isophane insulin before breakfast and a fixed mixture of 30% human soluble insulin and 70% human isophane insulin before the evening meal. The patients with Type 1 diabetes who received the insulin lispro mixture before breakfast had lower post-prandial blood glucose and lower pre-lunch blood glucose compared with those who received the human insulin mixture; the treatments did not differ with respect to HbA_{1c} and the incidence of hypoglycaemia.

To examine the premise that the addition of NPL to pre-meal insulin lispro may augment the action of insulin between meals, the administration of a fixed mixture of 50% insulin lispro and 50% NPL (Mix50) before meals was compared with pre-meal human soluble insulin (with isophane insulin being administered at bedtime in both treatment regimens) in a group of people with Type 1 diabetes. Thus, the aims of the present study were to compare the effects of Mix50 on pre- and post-prandial blood glucose concentrations, overall quality of glycaemic control, and frequency of hypoglycaemia, with those of pre-meal human soluble insulin in patients with Type 1 diabetes.

Patients and methods

Patients

One hundred and nine volunteers with Type 1 diabetes (aged 22 to 43 years) were recruited. Criteria for inclusion were Type 1 diabetes for > 2 years and good health, and an HbA_{1c} concentration at screening that was not more than 1.75 times the upper limit of the non-diabetic range for the local laboratory of each centre. The participants had to be self-monitoring their blood glucose and using a basal-bolus insulin regimen with pre-meal injections of either human soluble insulin or insulin lispro, supplemented by isophane insulin at bedtime, for at least 3 months before recruitment. Participants had to have regular meals, which included breakfast, lunch and an evening meal. Individuals were excluded if they had experienced two or more episodes of severe hypoglycaemia (requiring external assistance) within the preceding 3 months. The characteristics of the 109 participants are summarized in Table 1. All were Caucasian with the exception of one African. Eighty-nine completed both arms of the study (see protocol below). One patient was randomized but withdrew before receiving treatment. Nineteen discontinued the study because of protocol violations (Mix50, $n = 3$ and human soluble insulin, $n = 2$), adverse events (Mix50, $n = 2$), and patient and/or physician decision (Mix50, $n = 4$ and human soluble insulin, $n = 8$).

Table 1 Clinical characteristics at baseline (mean ± SD) of 109 participants with Type 1 diabetes by treatment sequence

	Mix50/human soluble insulin	Human soluble insulin/Mix50
Number	$n = 53$	$n = 56$
Sex: female/male	30/23	26/30
Age (years)	34.4 ± 9.8	31.4 ± 8.9
HbA_{1c} (%)	8.1 ± 1.2	7.9 ± 1.5
Weight (kg)	72.87 ± 12.52	70.93 ± 12.40
Body mass index (kg/m^2)	25.3 ± 3.4	24.3 ± 3.1
Duration of diabetes (years)	11.2 ± 7.2	11.0 ± 7.3
Duration of insulin therapy (years)	11.1 ± 7.3	11.0 ± 7.3

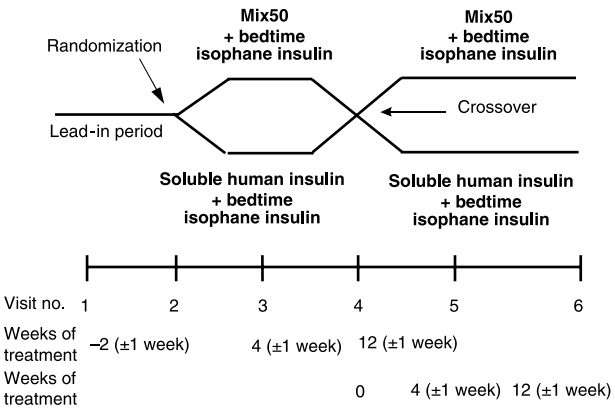

Figure 1 The crossover design of the study is shown to indicate treatment regimens and time of each treatment period.

Study protocol

The study protocol was approved by the local medical research ethics committee of all participating centres. The participants were asked to sign an informed consent document to participate in the study in accordance with the Declaration of Helsinki and good clinical practice guidelines.

The study was performed in 10 centres in Europe and South Africa and was a randomized, open-label, two-period, 24-week crossover comparison of two treatments. The study design is shown in Fig. 1. During a 2-week lead-in, the participants used pre-meal human soluble insulin (Humulin® S, Eli Lilly) and bedtime human isophane insulin (Humulin® I, Eli Lilly) as a standard basal-bolus regimen. The participants were then randomized to one of two treatment sequence groups. One group ($n = 53$) received a pre-meal insulin lispro mixture (Humalog® Mix50™, Eli Lilly) with isophane insulin at bedtime for the first 12 weeks, and after crossover received pre-meal human soluble insulin with isophane insulin at bedtime for the remaining 12 weeks. The other treatment group ($n = 56$) received the same treatments given in the reverse order.

Because of the different physical appearance of the insulins, differences in time–action profiles between human soluble insulin and the insulin lispro mixture, and the need to administer these insulins at different time intervals before meals, the study was open label. The protocol specified that the insulin lispro mixture should be injected between 0 and 5 min before meals, and human soluble insulin 30 min before meals. All insulin injections were given using a pen device (HumaPen®, Eli Lilly).

The dosing recommendations were based on the observations of dose requirements using Humalog® Mix50™ in a small pilot study of eight people with Type 1 diabetes [8], none of whom participated in the present study. When transferring from one treatment arm of the study to the other, it was recommended that the same total daily dose of insulin be used. When switching from pre-meal human soluble insulin to the pre-meal insulin lispro mixture, it was recommended that the pre-meal insulin doses remain the same before breakfast and lunch but that the dose of Mix50 should be increased before the evening meal while the dose of bedtime isophane insulin be decreased. As specified in the study protocol, the following recommendations for determining the initial insulin doses were considered by each investigator: (i) calculate the total daily insulin dose on the last day of the lead-in phase; (ii) use doses of insulin lispro Mix50 before breakfast and lunch, which are equivalent to the human soluble insulin doses on the last day of the lead-in phase; (iii) use a bedtime human isophane insulin dose which is 10% of the total daily dose on the last day of the lead-in phase; and (iv) the remainder of the daily dose be given as insulin lispro Mix50 before the evening meal to achieve the desired total daily dose. When transferring from the pre-meal insulin lispro mixture to the pre-meal human soluble insulin, it was recommended that the bedtime dose of isophane insulin be increased and the dose of human soluble insulin decreased before the evening meal, using the doses administered during the lead-in as a guide. The final choice of insulin dose was determined at the discretion of the investigator. The protocol required adjustment of insulin doses to achieve specific treatment goals: fasting, pre-lunch, pre-evening meal and bedtime blood glucose values < 7 mmol/l, and 2-h post-prandial blood glucose values < 10 mmol/l.

The participants were asked to perform eight-point blood glucose profiles on three non-consecutive days (one weekend day and two weekdays) in the week before randomization and in the final 2 weeks of each 12-week treatment period, using capillary blood glucose meters (AccuChek®, Advantage™, Boehringer Mannheim). The profile comprised blood glucose measurements before, and 2 h after, breakfast, lunch, and the evening meal, at bedtime and at 3:00 a.m. Average blood glucose values were used for analyses. It was estimated that a sample size of around 90 participants would be required to detect a significant difference in blood glucose of 1.0 mmol/l at the different times of measurement (two-sided test at significance level of 0.05 with 80% power). Additional blood glucose monitoring was advised for adjustment of insulin doses, particularly at the start of each treatment period, either at the discretion of the patient or on the advice of their clinician. The blood glucose profiles were recorded in a diary, along with insulin doses and times of administration, the time of each meal, and the number of snacks eaten between meals.

Participants recorded any episodes of hypoglycaemia, defined by a blood glucose < 3.0 mmol/l, or accompanied by subjective symptoms, or identified by signs noted by an observer that were considered to represent hypoglycaemia. At each patient visit, the rate of hypoglycaemia was computed as the number of hypoglycaemic episodes per patient adjusted for 30 days (episodes since previous visit/patient/30 days), and the frequency

Table 2 Baseline and endpoint insulin doses (U/kg) (mean ± SD) for various times of administration during treatment with Mix50 and human soluble insulin

	Baseline values	Mix50 + isophane	Human soluble insulin + isophane	*P*-value*
Pre-breakfast	0.14 ± 0.06	0.16 ± 0.07	0.15 ± 0.06	0.006
Pre-lunch	0.15 ± 0.05	0.17 ± 0.06	0.15 ± 0.05	< 0.001
Pre-evening meal	0.18 ± 0.06	0.28 ± 0.11	0.18 ± 0.06	< 0.001
Bedtime human isophane insulin	0.29 ± 0.11	0.16 ± 0.08	0.29 ± 0.12	< 0.001
Total pre-meal treatment	0.48 ± 0.15	0.62 ± 0.20	0.49 ± 0.14	< 0.001
Total (pre-meal + human isophane insulin)	0.76 ± 0.23	0.78 ± 0.23	0.76 ± 0.21	0.390

*Comparison between two treatments at endpoint.

was considered to be the number of hypoglycaemic episodes since the previous visit. Daytime (8 a.m. to 11 p.m.) and nocturnal (11 p.m. to 8 a.m.) hypoglycaemia frequency (average number of episodes per patient) and incidence (patients who experienced at least one hypoglycaemic episode) were also analysed for the entire treatment period for each treatment. Hypoglycaemia was considered to be severe if assistance by another person was required. The incidence of severe hypoglycaemia was also analysed for the entire treatment period for each treatment.

HbA_{1c} was analysed in a central laboratory using high-performance cation exchange chromatography (non-diabetic reference range 4.3–6.1%), before randomization, and at the end of each treatment period. Participants were asked to maintain their normal lifestyle, exercise, and diet (particularly the timing of meals) throughout the study.

Statistical analysis

The crossover study was designed to include approximately 108 patients in each treatment arm assuming a drop-out rate of about 16% to detect differences in pre-meal (morning, noon and evening) blood glucose (BG) concentrations. Data from a pilot study were used to estimate the overall SD to detect a difference of about 0.95 mmol/l in each of morning, noon and evening pre-meal BG concentrations. A two-sided test with $\alpha = 0.05$, with the estimated overall SD and a power of 80% was used to estimate the sample size for this study. Last observation carried forward (LOCF) was used to impute missing data within each period of the two-period crossover study. No data were carried forward from period 1 to period 2.

Efficacy and safety data from randomized patients who had at least one observation for both period 1 and period 2 were used to perform the crossover analysis. Parametric or non-parametric analyses for two-period crossover data were performed using methods as suggested previously [10–12]. Tests to detect unequal carryover effects for various efficacy and safety measures were performed. No unequal carryover effects were detected for any of the efficacy or safety measures. Non-parametric analyses were used only for hypoglycaemia variables. All comparisons were performed using two-tailed tests with a nominal significance level of 0.05. As per protocol, no adjustments for multiplicity were made in the analyses. Values are presented as mean ± SD, except when variables were not normally distributed and then median (interquartile ranges) instead of mean values were reported.

Results

Mean insulin dose and time of injection

As described in the protocol, any modifications in insulin dose that occurred during the study were determined by the protocol that gave recommendations for the initial insulin dose and further adjustments when switching regimens. The insulin doses during the treatment periods with Mix50 and human soluble insulin at different times of administration are shown in Table 2. The mean total insulin dose did not differ between the two treatments. However, the bedtime isophane dose was higher when patients were receiving human soluble insulin compared with Mix50. The total pre-meal treatment dose was higher for patients receiving Mix50 compared with human soluble insulin. The pre-meal insulin doses, although statistically different, were of similar magnitude before breakfast and lunch for both treatments. The insulin dose before the evening meal was higher with Mix50 than with human soluble insulin. The median reported injection time before meals was 4.2 min (25th percentile = 1.0 min; 75th percentile = 6.3 min) for the Mix50 and 24.6 min (25th percentile = 16.6 min; 75th percentile = 30.0 min) for human soluble insulin.

Blood glucose concentrations

Mean 24-h BG profiles are shown in Fig. 2. Pre-meal and bedtime BG concentrations did not differ between the regimens. The pre-meal target values for BG were not achieved with either treatment regimen. The only difference in BG between the two treatment arms was observed at 2 h after the evening meal, when glucose was lower with Mix50 than with human soluble insulin (8.4 ± 3.0 vs. 9.6 ± 3.5 mmol/l; $P = 0.049$). No differences were observed between the two treatment groups for BG at all other times of measurement, including those at 03.00 h. Mean BG (an average of the eight-point blood glucose profile) was comparable for the two treatments (Mix50 8.9 ± 1.9 vs. human soluble insulin 9.1 ± 2.0 mmol/l; $P = 0.581$).

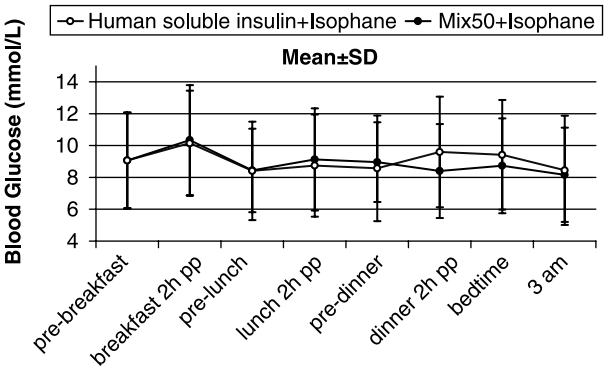

Figure 2 Mean (± SD) capillary blood glucose values are shown at the different time points measured throughout 24 h for each treatment regimen.

Haemoglobin A_{1c}

No difference in HbA_{1c} concentration was identified between the two treatments at the end of the 12-week treatment period (Mix50 8.1 ± 1.3% vs. human soluble insulin 8.2 ± 1.2%; *P* = NS).

Hypoglycaemia

No difference was observed between treatments in the frequency of hypoglycaemic episodes at endpoint (Mix50 4.8 ± 5.1 episodes/patient vs. human soluble insulin 5.1 ± 5.3 episodes/patient; *P* = NS). Similarly, the median rate of hypoglycaemia did not differ between the two treatments (Mix50 1.84, 25th percentile = 0.54; 75th percentile = 3.87 episodes/patient/30 days vs. human soluble insulin 2.12, 25th percentile = 0.51; 75th percentile = 4.20 episodes/patient/30 days; *P* = NS).

Neither the overall frequency of daytime hypoglycaemic episodes (Mix50 6.0 ± 7.7 episodes/patient vs. human soluble insulin 6.1 ± 7.0 episodes/patient; *P* = NS), nor of nocturnal hypoglycaemic episodes (Mix50 2.9 ± 3.6 episodes/patient vs. human soluble insulin 2.8 ± 3.8 episodes/patient; *P* = NS) was different between the two treatments. The number (percentage) of patients experiencing one or more episodes of hypoglycaemia (incidence) during the treatment period did not differ between treatments either for nocturnal hypoglycaemia, Mix50, 69 (67.0%) vs. human soluble insulin 71 (68.3%; *P* = NS) or daytime hypoglycaemia, Mix50, 88 (85.4%) vs. human soluble insulin 85 (81.7%; *P* = NS). The number of patients experiencing one or more episodes of severe hypoglycaemia (assistance required by another person) was not different (Mix50 6 [5.5%] vs. human soluble insulin 10 [8.8%]; *P* = NS).

Snacking

No specific advice was given to participants regarding the inclusion of snacks between meals, which was left to their individual choice. The median number of snacks per patient per day was comparable for the two treatments (Mix50 2.0, 25th percentile = 1.0; 75th percentile = 3.0 vs. human soluble insulin 1.8, 25th percentile = 1.0; 75th percentile = 3.0; *P* = NS). The number of snacks between breakfast and lunch, between lunch and the evening meal, between the evening meal and bedtime, and between bedtime and breakfast the following morning was similar for both treatments.

Weight

Body weight was comparable at endpoint for both treatments (Mix50 72.3 ± 11.9 kg vs. human soluble insulin 73.2 ± 12.7 kg; *P* = NS). Though not significantly different, the change in body weight from baseline for the Mix50 group was 0.3 ± 2.2 kg and 1.0 ± 2.2 kg for human soluble insulin (*P* = NS).

Discussion

Evaluation of intensive insulin regimens has suggested that the optimization of insulin dose of short and intermediate-acting insulins is necessary to achieve good glycaemic control as measured by HbA_{1c} [6,7,13,14]. The use of rapid-acting insulin analogues before meals lowers post-prandial blood glucose more rapidly than human soluble insulins and provides the potential for greater flexibility and convenience in timing of administration [2]. An additional benefit may be a lower frequency of hypoglycaemia, particularly during the night [2]. The supply of basal insulin throughout the day can be enhanced by combining insulin lispro with isophane insulin before meals, which improves glycaemic control in the late post-prandial phase [6,14,15]. When the use of pre-meal insulin lispro is compared with pre-meal human soluble insulin, in people with Type 1 diabetes, HbA_{1c} can be lowered, provided sufficient supplementary injections of isophane insulin are given to optimize glycaemic control [13,16]. This usually requires additional injections of insulin. In one study [16] the mean number of injections of isophane insulin per day was increased from 1.4 to 3.1 during the optimization phase with insulin lispro, and injections of isophane insulin were required before breakfast and lunch, in addition to that given at bedtime. One possible solution would be to give isophane insulin in combination with insulin lispro, as a fixed mixture, in every pre-meal injection.

In the present study, the use of a fixed mixture of 50% insulin lispro with 50% NPL (as Mix50) before every meal in a standard basal-bolus insulin regimen achieved a degree of glycaemic control equivalent to the use of pre-meal human soluble insulin. The blood glucose profiles indicated that injection of Mix50 immediately before meals provided a similar glucodynamic profile to human soluble insulin injected 30 min before meals. Glycaemic control did not deteriorate in the late post-prandial phase, suggesting that the NPL component of Mix50 provides a supply of basal insulin between meals equivalent to the time–action profile of pre-meal human soluble insulin. Plasma insulin concentrations were not measured in the present study.

Recommendations for the initial dose of insulin to be used when changing regimens were provided in the protocol, and

were based on observations from a previous pilot study [8]. Therefore, the insulin doses recorded and the associated blood glucose changes were in part protocol-driven, although the protocol also required further adjustment of the insulin dose during each treatment period to meet the metabolic targets of the study. The total daily insulin dose did not differ between treatments. Similar preprandial doses of Mix50, before breakfast and lunch, were associated with similar magnitudes of post-prandial blood glucose excursions after these meals as observed with human soluble insulin. The dose of the Mix50 that was administered before the evening meal was higher than the dose of human soluble insulin, and the mean post-prandial blood glucose after the evening meal was lower than with human soluble insulin. The rapid-acting insulin in the Mix50 limited the rise in post-prandial blood glucose while the basal component, maintaining insulin activity until the next meal, prevented preprandial hyperglycaemia. The quality of glycaemic control achieved by either treatment was moderate, and a limitation of the present study was that the pre-meal insulin doses were not optimized for the carbohydrate content of each meal. It is possible that higher doses of the Mix50 before breakfast and lunch would have decreased the blood glucose after these meals and may possibly have improved HbA_{1c}. The safety profile of Mix50 with respect to the frequency of hypoglycaemia did not differ from human soluble insulin. The protocol required that the participants maintained their normal lifestyle, exercise, diet and timing of main meals throughout the study. Thus, because flexibility of insulin administration was not possible, the results cannot be extrapolated to people with more variable lifestyles.

The use of fixed insulin mixtures has advantages and disadvantages that are well recognized in clinical practice. Many people inject human soluble insulin immediately before meals, which encourages the development of post-prandial hyperglycaemia. The presence of rapid-acting insulin in a fixed mixture such as Mix50 should confer an advantage in controlling post-prandial blood glucose. However, the mixing ratio of 50% of each insulin component as provided by Mix50 may not be optimal for every meal, the size and nature of which can vary considerably. In some cases and situations, the dose of rapid-acting insulin required to optimize control of post-prandial blood glucose may have to be higher than can be achieved with insulin lispro/NPL in a 50:50 mixture; increasing the dose of the fixed mixture could risk inducing late post-prandial hypoglycaemia as a result of excessive NPL. However, in some situations a fixed mixture containing a larger proportion of insulin lispro and a smaller proportion of NPL may be preferable.

Ciofetta *et al.* [14] reported lower post-prandial blood glucose values, and improved glycaemic control (HbA_{1c}) with insulin lispro than with human soluble insulin in people with Type 1 diabetes. In that study [14], the group treated with insulin lispro injected isophane insulin three to four times daily with the isophane component accounting for approximately 30%, 40%, and 10% of the total pre-meal insulin dose before breakfast, lunch, and evening meal, respectively. In another study [6] participants who were treated with insulin lispro mixtures using a ratio of 70/30 insulin lispro/NPL before breakfast, 60/40 before lunch, and 80/20 before the evening meal, achieved a lower mean HbA_{1c} concentration with less frequent hypoglycaemia compared with those treated with human soluble insulin alone. Finally, a fixed combination of insulin lispro and NPL at a ratio of 75/25 was compared with human soluble insulin as pre-meal insulin for a duration of 12–14 weeks [17]. This particular study demonstrated better post-prandial blood glucose with the insulin lispro/NPL mixture, but HbA_{1c} and the frequency of hypoglycaemia did not differ from human soluble insulin [17].

The use of pre-meal Mix50 in a basal-bolus regimen provides an alternative to giving human soluble insulin alone before meals. Although better glycaemic control was not obtained in the present study, use of this fixed mixture may simplify the administration of insulin therapy by allowing patients to inject immediately before meals.

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