TREATMENT OF TYPE 1 DIABETES WITH INSULIN LISPRO DURING RAMADAN

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SUMMARY
Objective: To compare insulin lispro with regular human insulin with respect to blood glucose control and frequency of hypoglycaemia in patients with type 1 diabetes who wished to fast during the month of Ramadan.

Research design and methods: Insulin lispro or regular human insulin was given together with NPH insulin, twice daily before the morning and evening meals, for two weeks each in an open-label, randomised, crossover design, and 64 patients completed the protocol. Blood glucose was self-monitored at fasting morning and evening, and 1-h and 2-h after the post-sunset meal on three consecutive days at the end of each treatment period.

Results: The 2-h blood glucose excursion after the post-sunset meal was significantly (p = 0.026) lower with insulin lispro (2.50 ± 0.46 mmol/l) than with regular human insulin (3.47 ± 0.49 mmol/l). Daily insulin doses did not differ between treatments but compliance with recommended time of injection was better with insulin lispro. Hypoglycaemia incidence (insulin lispro, 15 (23.4%) patients; regular human insulin 31 (48.4%) patients; p = 0.004) and frequency (insulin lispro, 0.70 ± 0.19; regular human insulin 2.25 ± 0.36 episodes/patient/30 days; p < 0.001) were lower with insulin lispro. Five (22.7%) of the episodes during insulin lispro occurred during the nocturnal period compared with 27 (36.5%) of the episodes while on regular human insulin.

Conclusions: Glycaemic control, measured by postprandial glycemic excursions, was improved and hypoglycaemia was significantly reduced with insulin lispro compared with regular human insulin. Patients with type 1 diabetes who insist on fasting during Ramadan may be better managed with insulin lispro.

Key-words: insulin lispro, insulin analogue, Ramadan, fasting, type 1 diabetes.

RÉSUMÉ - Traitement du diabète de type 1 par insuline lispro au cours du Ramadan.

Objectif: Comparer l'insuline lispro et l'insuline rapide en termes d'efficacité et de fréquence des hypoglycémies chez des diabétiques de type 1 souhaitant jeûner pendant le mois de Ramadan.

Matériel et méthodes: L'insuline lispro ou l'insuline rapide a été associée à la NPH, de deux fois par jour avant les repas du matin et du soir, pendant 2 semaines chacune dans une étude ouverte randomisée en crossover, 64 patients ayant mené à bout le protocole. L'autosurveillance a porté sur la glycémie du matin à jeûn et du soir, et 1 h et 2 h après le repas suivant le coucher du soleil pendant 3 jours consécutifs à la fin de chaque période thérapeutique.

Résultats: L'excursion glycémique 2 h après le repas suivant le coucher du soleil était significativement (p = 0.026) plus basse sous lispro (2,50 ± 0,46 mmol/l) que sous insuline rapide (3,47 ± 0,49 mmol/l). Les doses quotidiennes d'insuline n'étaient pas différentes mais la compliance vis-à-vis de l'heure recommandée d'injection était meilleure avec la lispro. L'incidence des hypoglycémies (insuline lispro, 15 (23,4 %) patients ; insuline rapide, 31 (48,4 %) patients ; p = 0,004) et la fréquence (insuline lispro, 0,70 ± 0,19 ; insuline rapide 2,25 ± 0,36 épisodes/patient/30 jours ; p < 0,001) étaient plus basses sous lispro. Cinq (22,7 %) des épisodes sous lispro sont survenus pendant la période nocturne contre 27 (36,5 %) des épisodes sous insuline rapide.

Conclusions: Le contrôle glycémique, mesuré par les excursions glycémiques post-prandiales, est amélioré et l'hypoglycémie significativement réduite sous insuline lispro par rapport à l'insuline ordinaire. Les diabétiques de type 1 qui tiennent à jeûner pendant le Ramadan peuvent tirer avantage de l'insuline lispro.

Mots-clés: insuline lispro, analogue de l’insuline, Ramadan, jeûne, diabète de type 1.

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Ramadan is the ninth lunar month of the Islamic year and fasting during the month is one of the five pillars of Islam. It is obligatory for all healthy adults of the Islamic faith to fast between the hours of dawn and sunset. Although certain people, including those with serious illness, are exempt, many patients with diabetes insist on following the fast, often without informing the treating physician or obtaining proper instructions [1, 2]. Depending on geographical area and time of year when Ramadan occurs, the fast is approximately 11 to 19 hours per day. No food or drink is taken during sunlight hours and the main meals are taken before sunrise (Sahur) and after sunset (Iftar). There may also be abstention from oral and injected medications and, in some cultures, from withdrawal of blood.

As well as the change in dietary pattern there may be a change in content, with increased intake of fat and carbohydrates [3]. These changes in dietary habits present serious problems for patients with diabetes [1, 4] and glycaemic control deteriorates [5, 6]. There is often excessive intake at the evening meal resulting in hyperglycaemia [7]. During daylight hours hypoglycaemia is a particular problem when patients do not want to take snacks. They may try to compensate for fasting by reducing the morning dose of insulin but this may then result in hyperglycaemia.

Optimisation of insulin therapy during Ramadan fasting is, therefore, essential to try to control both hyperglycaemia and hypoglycaemia. However, very few studies have examined insulin treatment of patients with diabetes during Ramadan. In patients with type 1 diabetes, short-acting insulin before meals and intermediate-acting insulin given late evening has been used safely [8]. A recent study [9] of patients with type 2 diabetes during Ramadan reported better glycaemic control during insulin lispro treatment compared with regular human insulin. The present multinational study was carried out to compare efficacy and safety of insulin lispro and regular human insulin in the treatment of patients with type 1 diabetes who wished to fast during Ramadan.

## Patients and Methods

This open-label comparative crossover study was carried out with appropriate ethical approval at six centres in Saudi Arabia, United Arab Republic, Kuwait, Pakistan, Egypt and Morocco. After being informed about the legitimacy of abstaining from fasting, all patients confirmed that they wanted to follow Ramadan and gave written informed consent for study participation. The study involved 67 patients with type 1 diabetes mellitus who had received twice daily insulin treatment for at least 2 months prior to entry. Patients were not included if they had vascular disease, retinopathy, renal impairment, liver disease, insulin resistance defined as daily insulin dose > 2 units/kg or a history of clinically significant hypoglycaemia unawareness.

During the study, patients attended the clinic for four visits, starting at one month before Ramadan. At the first visit, baseline demographic data was collected and each patient was trained to carry out glucose measurements using a glucose meter (Accutrend, Boehringer Mannheim, Germany). Patients continued to use twice daily insulin treatments, consisting of soluble insulin plus intermediate-acting insulin, given morning and evening before breakfast and dinner, respectively, during the run-in period. One day prior to the start of Ramadan, patients returned for the second clinic visit at which time they were randomised to one of two treatment sequences. The sequences consisted of either insulin lispro (Humalog®, Eli Lilly and Company, Indianapolis, IN, USA) or regular human insulin (Humulin® R, Eli Lilly and Company) for two weeks, followed by the alternate treatment for a further two weeks. The insulin lispro or regular human insulin was given, together with intermediate-acting insulin (Humulin® N, Eli Lilly and Company), twice daily before the morning and evening meals throughout the one-month period of Ramadan. Patients returned for clinic visits at the cross-over point when the soluble insulin treatment was changed, and at the endpoint of the study.

The study was carried out on an open-label basis in order for the insulin lispro and regular human insulin to be administered at the recommended times before meals. Patients were instructed to administer insulin lispro, together with the NPH insulin, immediately before starting a meal, whereas regular human insulin, together with the NPH insulin, was to be given 30 minutes before starting a meal. The soluble and NPH insulins were supplied either in pen devices or in vials with syringes and patients were instructed to mix the soluble and NPH insulins in syringes immediately before administration. The dosage regimen could be adjusted by investigators in accordance with the metabolic needs of the patients. However, when changing treatments patients were advised to start the new treatment on the same insulin dose as that used just prior to the change. Investigators recommended regular self-monitoring of blood glucose according to their usual practice and this was used as the basis for insulin dose adjustments.

On three consecutive days at the end of each two-week treatment period, patients were asked to record glucose profiles using the Accutrend glucose meters. Glucose determinations were not taken between the hours of sunrise and sunset in order to respect those patients who considered that withdrawal of blood was contrary to the religious practice of the fast. This precluded postprandial measurements after the morning meal so a simplified 4-point profile was used. Capillary blood glucose was determined while fasting.
before sunrise, fasting after sunset and at 1-h and 2-h postprandial after the evening meal.

On the days when glucose profiles were determined, the glucose values, insulin doses and timing, and the times of each meal were recorded by the patients in study diaries. Hypoglycaemic episodes were also recorded in the diaries throughout the study. Hypoglycaemia was defined as any time a patient felt, or another person observed, signs or symptoms associated with hypoglycaemia, or a blood glucose measurement less than 3.0 mmol/l (54 mg/dl).

The blood glucose profiles determined on the three consecutive days were averaged across days for each patient. Blood glucose excursions were calculated from the differences between the 1-h or 2-h postprandial values and the respective fasting after sunset value. All data are expressed as mean ± SEM. The two insulin treatments were compared using an analysis of variance model for a crossover design to evaluate both carryover and treatment effects. No evidence for a statistically significant carryover effect was found for any of the variables analysed. Treatment effects for categorical variables such as frequency of hypoglycaemia were determined using a chi-square test or Fisher’s exact test.

■ RESULTS

Patients

Of the 67 patients enrolled in the study, 64 (95.5%) completed the study protocol. Two patients discontinued early from the study at their own request and the third patient due to repeated hypoglycaemic episodes. The baseline characteristics of the 64 patients who completed the study are summarised in Table I. There were no significant differences between the two treatment sequences for any of the characteristics. For all 64 patients the mean age was 31.8 ± 1.3 years, ranging from 14.9 to 59.4 years, the mean duration of diabetes was 8.7 ± 1.0 years, ranging from 0.5 to 35.0 years and mean duration of insulin treatment was 8.2 ± 1.0 years, ranging from 0.2 to 35.0 years.

Blood Glucose Control

The mean values for the blood glucose levels from the self-monitored profiles at the end of each treatment are shown in Table II. The fasting values were slightly lower with regular human insulin than with insulin lispro, particularly before sunrise when the mean fasting values were significantly different (p = 0.046). The mean 1-h and 2-h postprandial values after the evening meal were slightly higher with regular human insulin but the differences between treatments were not significant. The postprandial excursions calculated as the difference between postprandial and fasting values are shown in Figure 1. The excursion at 1-h after the evening meal was slightly lower with insulin lispro but the difference did not reach significance. However, at 2-h after the evening meal the excursion was significantly (p = 0.026) lower with insulin lispro (2.50 ± 0.46 mmol/l) than with regular human insulin (3.47 ± 0.49 mmol/l).

Insulin Dose and Administration

There were no significant differences between the two treatments in daily dose of soluble insulin (insulin lispro, 0.39; regular human insulin, 0.38 U/kg), NPH
insulin (insulin lispro, 0.44; regular human insulin, 0.45 U/kg) or total insulin (insulin lispro, 0.83; regular human insulin, 0.83 U/kg). There were 24 (37.5%) patients who required snacks during insulin lispro treatment compared with 30 (46.9%) patients during regular human insulin treatment, but the extra insulin required for the snacks was not different (0.10 U/kg for each). During the insulin lispro treatment period, patients were instructed to inject the insulin just prior to meals and 82% of patients stated that they injected it 0-10 min before meals. During the regular human insulin period, patients were instructed to administer the insulin 30 min before meals. However, only 54% complied with this and 28% stated they injected it 11-20 min before the meal while 16% stated they injected it 0-10 min before.

### Hypoglycaemia

During the Ramadan period there were 15 (23.4%) patients who experienced hypoglycaemia while on insulin lispro compared with 31 (48.4%) patients while on regular human insulin, and the difference between treatments was significant (p = 0.004). The calculated mean rate of hypoglycaemic episodes was also significantly less with insulin lispro (0.70 ± 0.19 versus 2.25 ± 0.36 episodes/patient/30 days; p < 0.0001). The total number of hypoglycaemic episodes during each treatment was 22 with insulin lispro and 74 with regular human insulin. The distribution of hypoglycaemic episodes throughout the day is shown in Figure 2. Between 6 h after breakfast and the start of the sunset meal, 11 episodes occurred during the insulin lispro treatment while 27 episodes occurred during regular human insulin treatment. During the nocturnal period, from 6 h after dinner until the start of the sunrise meal, the number of episodes and percent of the total were less with insulin lispro (5 (22.7%) episodes) than with regular human insulin (27 (36.5%) episodes).

### DISCUSSION

Type 1 diabetes mellitus is a life-long disease that requires insulin treatment every day. Despite this, the aim of therapy is to try to minimise the impact of the disease and ensure that the lifestyle of the patient is as near normal as possible. For Muslims a normal lifestyle includes being able to follow their religious convictions which means fasting during the month of Ramadan. Those with chronic illnesses are exempt from fasting yet many insist on following the fast.

### TABLE II

Self-monitored blood glucose profiles determined at the end of 2 weeks of treatment with either insulin lispro or regular human insulin during Ramadan.

<table>
<thead>
<tr>
<th>Mean blood glucose (mmol/l)</th>
<th>Insulin lispro</th>
<th>Regular human insulin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening fasting</td>
<td>9.01 ± 0.51</td>
<td>8.49 ± 0.44</td>
<td>0.202</td>
</tr>
<tr>
<td>Evening 1-h postprandial</td>
<td>12.17 ± 0.48</td>
<td>12.30 ± 0.40</td>
<td>0.715</td>
</tr>
<tr>
<td>Evening 2-h postprandial</td>
<td>11.54 ± 0.47</td>
<td>11.90 ± 0.42</td>
<td>0.279</td>
</tr>
<tr>
<td>Morning fasting</td>
<td>8.99 ± 0.43</td>
<td>8.13 ± 0.42</td>
<td>0.046</td>
</tr>
</tbody>
</table>

**Fig. 1.** One hour and two hour blood glucose excursions following the post-sunset meal at the end of treatment with either insulin lispro or regular human insulin during the month of Ramadan. * P = 0.026 for insulin lispro compared with regular human insulin.

**Fig. 2.** Distribution of hypoglycaemic incidence throughout the day with insulin lispro and regular human insulin treatments during Ramadan. Bars represent numbers of patients experiencing hypoglycaemia with number of episodes shown above.
Very little information is available regarding glycaemic control of patients with diabetes who wish to fast. Only one previous study of type 1 diabetes could be found in published literature and this examined just 11 patients [8]. The present study in 64 patients with type 1 diabetes compared use of insulin lispro with regular human insulin as the soluble insulin administered before meals. The randomised crossover design ensured that all patients received each treatment for two weeks of the Ramadan fasting period. The 2-h blood glucose excursion after the post-sunset meal was significantly lower with insulin lispro than with regular human insulin.

During Ramadan, dietary patterns are changed such that two meals are taken each day, at sunset and before sunrise. While patients with diabetes are generally advised to avoid meals with a high content of easily-absorbed carbohydrates, the evening meal often contains excessive carbohydrate and sugary liquids [3]. The pharmacokinetic profile of insulin lispro is better suited to cope with such meals and in non-fasting patients blood glucose excursions are reduced while on insulin lispro compared with regular human insulin [10]. In order to comply with the fast, patients often simply modify their intake of medications such that none are taken during daylight hours. To be able to eat as soon after sunset as possible patients would have to inject regular human insulin during daylight. Also, in the morning they would have to rise particularly early to administer regular human insulin and still have time to eat before sunrise. As a result, compliance with advised timing between regular human insulin and meals is poor. The rapid absorption of insulin lispro means that it can be injected immediately before meals so compliance with timing is much better.

One of the major worries of patients with diabetes, particularly when fasting, is the occurrences of hypoglycaemia [1]. Counter-regulatory mechanisms are altered in patients with type 1 diabetes, with a decreased peripheral counter-regulatory response to hypoglycaemia [11]. Both incidence and frequency of hypoglycaemia were significantly reduced with insulin lispro during Ramadan fasting in the present study. When analysed by time of day, there was a reduction in incidence from 6-h after the morning meal to the start of the post-sunset meal. There was also a large reduction in nocturnal incidence of hypoglycaemia, from 6-h after the post-sunset meal to the pre-sunrise meal. In studies of non-fasting patients, post-absorptive hypoglycaemia has been shown to be reduced with insulin lispro compared with regular human insulin [12] and awareness and counter-regulation were improved [13]. A significant reduction in nocturnal hypoglycaemia with insulin lispro in type 1 diabetes patients has also been reported [14].

In managing diabetes during Ramadan, health practitioners need to be able to advise patients how best to fulfil religious obligations without endangering their health. The results of this study indicate that fasting by patients with type 1 diabetes may be achieved by use of twice daily administration of rapid-acting insulin lispro in combination with an intermediate-acting insulin. As well as applying to Islamic patients with diabetes, such data are relevant to non-Islamic patients and appropriate doses of rapid-acting insulin can be used to establish glycaemic control in other situations that involve erratic eating behaviour. Use of insulin lispro decreased blood glucose excursions after the evening meal and produced a significant reduction in hypoglycaemia. Compliance with timing of treatment was also improved. Therefore, use of insulin lispro may encourage patients to discuss the problem of fasting with their physician rather than simply avoiding attendance at the clinic.

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