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Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan

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Abstract

Aims To compare insulin lispro with soluble human insulin in patients with Type 2 diabetes mellitus fasting during Ramadan, with respect to the rate of hypoglycaemic episodes and postprandial blood glucose values after the main meal after sunset.

Methods The insulins were compared in an open-label, randomized, cross-over study of 70 outpatients. Hypoglycaemic episodes were recorded by the patients in a self-monitoring diary. Fasting, 1-h and 2-h postprandial blood glucose values were recorded by the patient on three consecutive days at the end of each treatment period.

Results The fasting blood glucose values before sunrise ($P > 0.4$) and after sunset ($P > 0.6$) were similar and did not differ significantly between both treatment groups. The rise in blood glucose after the main meal after sunset was 3.0 ± 0.4 mmol/l after 1 h in the insulin lispro treatment group compared to 4.3 ± 0.4 mmol/l in the soluble insulin treatment group ($P < 0.01$), and 2.6 ± 0.4 mmol/l after 2 h with insulin lispro compared to 4.0 ± 0.5 mmol/l with soluble insulin ($P < 0.008$). Mean hypoglycaemic episodes per patient over 14 days were 1.3 ± 0.1 vs. 2.6 ± 0.2, $P < 0.002$, respectively, for insulin lispro and soluble insulin. Most hypoglycaemic episodes occurred during the time period from 6 h after the before sunrise meal until breaking the fast after sunset.

Conclusions The significantly lower rate of hypoglycaemic episodes combined with better control of postprandial blood glucose suggest insulin lispro may be more suitable prandial insulin for patients treated with Type 2 diabetes who fast during Ramadan.

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Keywords fasting, insulin, Lispro, Ramadan

Introduction

About 1 billion people worldwide are followers of Islam. A basic principal of Islam that is strictly observed is Ramadan, involving a fast from dawn to sunset for one lunar month. During the approximately 11–19 h of each day's fasting (the duration depends on the time of the year when Ramadan occurs and geographical location of the observer), the individual must abstain from taking food and drinks.

This poses obvious problems for patients with diabetes [1,2], who mostly prefer not to accept the exemptions allowed by Islam for patients with serious illnesses [3].

During Ramadan, patients treated with insulin have difficulty maintaining glucose control [4]. In order to avoid breaking the fast with snacks and drinks during the day, patients try to avoid hypoglycaemia by reducing their

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morning insulin dose. However, this may result in hyperglycaemia. The main meal after breaking the fast often leads to excessive gorging that may result in hyperglycaemia [3]. Consequently, Ramadan is often approached with fear, mostly of hypoglycaemia, by patients with diabetes as well as their treating physicians.

Insulin lispro, a human insulin analogue (insulin lispro or Humalog®), is a fast-acting insulin that can be administered immediately before a meal, enabling the patient to adjust their insulin dose to the actual meal. Use of insulin lispro results in a lower rise in postprandial blood glucose and improves patient quality-of-life by decreasing the frequency and severity of hypoglycaemia [5–9].

This cross-over study was designed to examine the effects of insulin lispro and soluble human insulin on the rates of hypoglycaemia and on postprandial blood glucose values after the main meal taken by diabetic patients after sunset during the fasting month of Ramadan.

Patients and methods

The design of this study was a randomized, cross-over, open-label, comparative study involving 70 outpatients. The cross-over study design was chosen in order to have each patient as their own control. As all patients had to have their visits at the same time, the 70 patients were allocated to seven different sites in order to ensure that the investigator would not need to handle more than 8–12 patients a day. The participating sites were: Naser Institute, Cairo, Egypt; King Khalid University Hospital, Riyadh, Saudi Arabia; King Fahad National Guard Hospital, Riyadh; Amiri Hospital, Kuwait; Jazira Hospital, Abu Dhabi, United Arab Emirates; Jinnah Postgraduate Medical Centre, Karachi, Pakistan; and the Akram Medical Complex, Lahore, Pakistan. Patients with Type 2 diabetes mellitus who had received therapy with human insulin for at least 2 months prior to entering the study were eligible to participate. The study was conducted in accordance with the guidelines of 'Good Clinical Practice' and the declaration of Helsinki, and was approved by the ethics committee of each participating centre.

Patients were required to attend four visits while participating in this 2-month trial. One month before the start of Ramadan (visit 1), the patient was educated on performing his/her own glucose measurements (Accutrend; Boehringer Mannheim, Mannheim, Germany), and the correct use of the patient diary. Patients were randomized at visit 2, one day before the start of Ramadan. The treatment sequence consisted of insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) or human soluble insulin (Humulin R; Eli Lilly) for 2 weeks followed by therapy with soluble insulin or insulin lispro for an additional two weeks (visit 3). Randomization lists were generated such that there were approximately an equal number of patients in each treatment sequence, and such that the investigator did not know the treatment sequence assignment of the next patient until the patient number had been assigned.

The study was not blinded to allow insulin lispro or soluble insulin to be given at the recommended time intervals before the meal. Patients were advised to inject either insulin lispro immediately before the meal or soluble insulin 30 min before the meal. Humulin NPH (Eli Lilly) was used as basal insulin. Patients administered their insulins with a pen-device or a syringe. Basal insulin was given twice a day together with insulin lispro or soluble insulin before the meal after sunset and before the meal before sunrise. Patients were allowed to mix fast-acting and basal insulin in the syringe at the time of the injection. At the time of treatment change, the patient was advised to start the new treatment period administering the same previously-used insulin dose. Daily self-monitoring of blood glucose was based on the clinical direction of the investigator as was the usual practice and served as the basis for insulin dose adjustments. The daily self-monitored blood glucose values, self administered insulin doses, and time of the dose were recorded during the whole study period by the patient in a diary and served to calculate insulin dose changes.

Patients were asked to perform a specific 4-point glucose profile using the same home glucose meter (Accutrend) on three consecutive days at the end of each 2-week treatment period. The profile consisted of capillary blood glucose measurement, collected at the time of fasting before sunrise, fasting after sunset and 1-h and 2-h postprandial after sunset. Glucose measurements during the daily fasting period were not requested and therefore were not recorded in order to respect some patients' religious objections to withdrawing blood during the fasting period.

Postprandial glucose values at the main meal after sunset were compared between the two treatments within the same patient. Blood glucose excursions were compared between the two treatments by estimating the difference between 1-h and 2-h postprandial blood glucose values and the fasting blood glucose value. Hypoglycaemic episodes were recorded by the patient in a self-monitoring diary. A hypoglycaemic episode was defined as any time a patient felt, or another person observed, that he/she was experiencing a symptom which they associated with hypoglycaemia, or a blood glucose measurement less than 3.5 mmol/l.

Patients or guardians signed an informed consent stating that they were willing to follow Ramadan fasting even after being informed about their legitimacy of abstention from fasting.

The within treatment comparison was performed using a paired Student's *t*-test (cross-over design). A cross-over model was used to evaluate both the carry-over and the treatment effect. Separate analyses of variance models (PROC ANOVA in SAS) were used to examine the carry-over and treatment effects. The overall test for treatment effects was performed using a chi-square test or Fisher's exact test for homogeneity. The frequencies within each category by visit and endpoint between the two sequence groups were compared using a chi-square test or Fisher's exact test. No evidence of statistically significant carry-over effect was detected, so no carry-over data are presented in the results. All results are expressed as means ± SE.

Results

Patients

A total of 70 patients were enrolled into the study. Fifty-seven (81%) patients completed the trial in accordance with the protocol. The reasons for early discontinuation were violation of entry criteria (five patients), patient

Table 1 Patient characteristics at visit 2

	Sequence 1 insulin lispro/soluble	Sequence 2 soluble/insulin lispro	All
n	33 (48.5%)	35 (51.5%)	68
Sex			
Male	17 (57.1%)	21 (60.0%)	38 (55.9%)
Female	16 (48.5%)	14 (40.0%)	30 (44.1%)
Age (years)*	50.5 ± 1.6	50.2 ± 1.5	50.3 ± 1.1
BMI (kg/m^2)*	28.6 ± 0.9	28.0 ± 0.9	28.3 ± 0.6
Duration of diabetes (years)*	11.5 ± 1.1	11.7 ± 1.0	11.6 ± 0.7
Duration of insulin treatment (years)*	5.3 ± 0.9	3.3 ± 0.7	4.2 ± 0.6

Treatment sequence consisted of pre-meal dose therapy (applied before the meal before sunrise and after sunset) with insulin lispro for 2 weeks followed by pre-meal dose therapy with soluble insulin for an additional 2 weeks (sequence 1) or vice versa (sequence 2). Not included are two drop-outs (patients' decisions) after Visit 1.
*Mean values ± SE.

decision (two patients before visit 2), protocol violations (five patients) and in one case an adverse event (hepatitis). Table 1 displays the characteristics of the patients involved in the study. There was no difference in mean body weight between the sequence groups. The mean body weight for the combined treatment groups was 76.5 ± 1.7 kg with insulin lispro and 76.6 ± 1.7 kg with soluble insulin.

Insulin administration

Daily insulin doses and number of injections of short and intermediate-acting insulin remained almost identical for both treatment groups. In both treatment groups the patient injected twice daily short-acting and intermediate-acting insulin. Twenty per cent of the patients delivered an additional short-acting insulin dose during additional late night meals. The frequency of the additional short-acting insulin doses was the same for both treatment groups ($n = 12$, 0.1 IU/kg). The time interval reported by the patients between injection and beginning of the meal was on average 4.8 ± 0.6 min for insulin lispro and 20.2 ± 1.2 min for soluble insulin. The mean total daily short-acting insulin was 0.27 ± 0.02 IU/kg for the insulin lispro treatment group and 0.28 ± 0.02 IU/kg for the soluble insulin treatment group, while the mean daily intermediate-acting insulin dose was 0.44 ± 0.03 IU/kg and 0.45 ± 0.03 IU/kg in each treatment group, respectively.

Although that the patients were advised at the time of switching the treatment to start by administering the same insulin dose used before the switch, a slight decrease was detected during the insulin lispro treatment in the insulin lispro dose (0.27 ± 0.02 U/kg) and an increase in the intermediate acting insulin dose of 0.01 IU/kg, respectively, compared to the soluble insulin treatment period (soluble dose 0.28 ± 0.02 U/kg). These did not achieve statistical significance

Blood glucose measurements

The fasting period lasted approximately 12–13 h depending on the geographical location. The fasting blood glucose values before sunrise and after sunset for the combined treatment groups were similar and did not differ significantly between both treatment groups as shown in Table 2. The insulin lispro treatment group showed a significant difference in both 1-h and 2-h postprandial blood glucose values after the main meal after sunset compared to the soluble insulin treatment group. The rise in blood glucose after the main meal after sunset at the endpoint for the two sequence groups combined was 3.0 ± 0.4 mmol/l after 1 h in the insulin lispro treatment group compared to 4.3 ± 0.4 mmol/l in the soluble insulin treatment group ($P < 0.01$). Two hours after the main meal after sunset, blood glucose was 2.6 ± 0.4 mmol/l with insulin lispro compared to 4.0 ± 0.5 mmol/l with soluble insulin ($P = 0.008$). No statistically significant carry-over effect was observed.

Hypoglycaemia

No severe cases of hypoglycaemia, defined as inability to self-treat, lethargy, or unconsciousness, were reported during this study. A total of 25 (44.6%) patients recorded their hypoglycaemic episodes. Ninety-six per cent of the recorded hypoglycaemic episodes were confirmed by hypoglycaemic signs/symptoms and blood glucose measurement. The number of patients with hypoglycaemic episodes was similar for both treatment groups (insulin lispro, $n = 16$; soluble insulin, $n = 19$) and sequence groups (soluble insulin/insulin lispro sequence, $n = 19$; insulin lispro/soluble insulin sequence, $n = 18$). However, patients had hypoglycaemic episodes more frequently during treatment with soluble insulin than during treatment with

Table 2 Blood glucose values for the combined treatment groups

Blood glucose values (mmol/l)	Insulin lispro*	Soluble insulin*	Treatment comparison for the mean on therapy
Fasting before sunrise	9.4 ± 0.4	9.8 ± 0.4	$P > 0.4$
Fasting after sunset	7.7 ± 0.3	7.9 ± 0.3	$P > 0.6$
1-h postprandial after sunset	10.2 ± 0.4	11.7 ± 0.4	$P < 0.01$
2-h postprandial after sunset	10.3 ± 0.4	12.0 ± 0.5	$P < 0.01$

*Mean values ± SE.

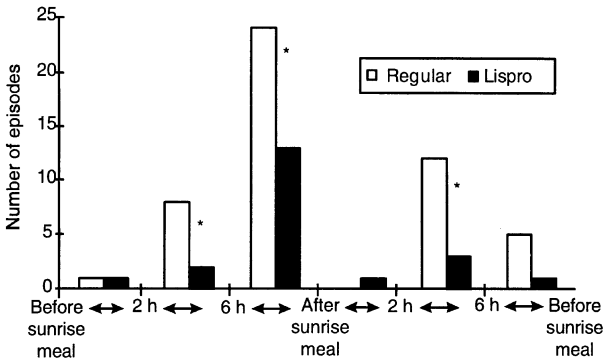

Figure 1 Distribution of the total number of hypoglycaemic episodes throughout the day over the course of the entire study for combined insulin lispro and soluble insulin treatment groups. *$P < 0.05$.

insulin lispro. Mean hypoglycaemic episodes per patient per 14 days were 1.3 ± 0.1 vs. 2.6 ± 0.2 ($P < 0.002$), respectively, for insulin lispro and soluble insulin. The total number of hypoglycaemic episodes during the study was 22 (30.1%) with insulin lispro treatment vs. 51 (69.9%) with soluble insulin treatment.

The total number of hypoglycaemic episodes distributed throughout the day over the course of the entire study are shown in Fig. 1. The majority of hypoglycaemic episodes (54%) occurred during the time period from six hours after the meal before sunrise until breaking the fast after sunset. Twenty-five per cent of the patients with soluble insulin treatment vs. 14% of the patients with insulin lispro treatment reported hypoglycaemic episodes during this time period. There was a higher frequency of hypoglycaemic episodes during the second period of the day. Between 2 and 6 h after the meal taken after sunset, the hypoglycaemic incidence was 5.2% in insulin lispro-treated patients compared with 14% in soluble insulin-treated patients.

Adverse events

There were no differences in type and frequency of adverse events between treatments. A total of six (including one hospitalization) patients reported adverse events: three during treatment with insulin lispro (pruritus, abnormal taste perception, worsening of existing depression) and two during treatment with soluble insulin (pruritus, gynaecomastia). In addition, one patient was hospitalized as a result of hepatitis during soluble insulin treatment. This patient discontinued treatment.

Discussion

Islam clearly exempts seriously ill patients from fasting during Ramadan, but the majority of Muslims with diabetes wish to observe the annual fasting. Previously, some clinicians thought it was unsafe for patients with diabetes to fast [10], but recent studies indicate that patients can achieve acceptable metabolic control while fasting [4,11].

In the present study, the treatment approach of two short-acting (soluble insulin or insulin lispro) and an intermediate-acting insulin (NPH) dose before sunrise and after sunset did not show any significant difference in the fasting blood glucose values before sunrise and after sunset. The multi-centre nature of the trial and the short duration of the observation periods precluded the analysis of HbA_{1c} data but the glucose data suggest no change in overall glucose control.

The treatment difference between insulin lispro and soluble insulin, under this dosing schedule, was the significant decrease of hypoglycaemic episodes with insulin lispro, mainly during the fasting hours of the day. This result suggests that, under fasting conditions, the unphysiological pharmacokinetics of soluble insulin, which may last 8–12 h [12] and with a late long-lasting insulin peak starting 2 hours after insulin administration, resulted in late postprandial hypoglycaemic episodes which were even aggravated under fasting conditions.

Jacobs *et al.* [13] suggested that, owing to the specific pharmacokinetics of insulin lispro (lasting 4–5 h with a sharp insulin peak after 1 h), it might control postprandial hyperglycaemia without enhancing the risk of late hypoglycaemia. This difference in pharmacokinetic profiles of the two insulins under strict fasting conditions, as during Ramadan, may indeed be the reason for the significant differences seen in the number of hypoglycaemic episodes between both treatment groups. The significant decrease of hypoglycaemic episodes with insulin lispro is of extreme

importance for fasting patients during Ramadan who are reluctant to control episodes of hypoglycaemia during the day through drinks or snacks as this would mean breaking the fast.

Poor dietary compliance by patients with diabetes is well documented [14]. The gorging behaviour after breaking the fast is understandable by anyone who has followed Ramadan. The tendency by many to consume more carbohydrates in the form of sweets during the holy month of Ramadan [15,16] makes it particularly difficult to control postprandial blood glucose after breaking the fast. Although patients in the present study were carefully instructed in dietary regimens for the fasting month, the high postprandial blood values after the main meal after sunset indicate the difficulties adhering to a strict diet. Heinemann *et al*. [17] showed a significant decrease of postprandial blood glucose after a high caloric and carbohydrate-rich test meal with insulin lispro in comparison to soluble insulin. In the present study, the significant 1-h and 2-hour decrease of the blood glucose of patients treated with insulin lispro compared to soluble insulin showed the effectiveness of insulin lispro to decrease postprandial glucose excursion under the 'normal' day-to-day dietary habits of patients fasting during Ramadan.

An additional advantage of lispro relates to the recommended time of injections. Difficulty in following optimal timing for soluble insulin administration before meals provides an additional challenge to the patient fasting during Ramadan. It implies waking even earlier before the meal taken before sunrise and the timing of the evening insulin dose is difficult because of religious and social activities occurring before the main meal after sunset.

The current study indicates that metabolic control in patients with Type 2 diabetes fasting during Ramadan can be achieved with a twice daily short and intermediate-acting insulin dose as long as proper self-monitoring and close professional supervision is guaranteed. The data suggest that treating diabetes during the fasting month of Ramadan may be easier with insulin lispro than with human soluble insulin, with better postprandial blood glucose control and fewer hypoglycaemic episodes. The use of insulin lispro will facilitate the long fasting and make it easier for Muslims with diabetes to follow Ramadan.

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Appendix

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