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Long-term efficacy of Humalog® in subjects with Type 1 diabetes mellitus

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Abstract

Aims To evaluate the long-term effectiveness of Humalog® insulin in lowering post meal glucose excursions.

Methods Twenty young subjects with Type 1 diabetes mellitus (DM) who had received insulin-lispro (Humalog®) for a least 1 year (mean ± SD 1.8 ± 1.6 years) were studied on two occasions, 3–14 days apart. They consumed a similar breakfast consisting of 450–600 kCal having fasted overnight. The same amount of human soluble Humulin® Regular or Humalog® insulin was given 10 min before the meal in a randomized, double-blind fashion.

Results Postprandial glucose excursions at 30, 60, and 120 min were significantly lower ($P < 0.001$, ANCOVA) when subjects received Humalog® as compared to human soluble insulin. Serum-free insulin levels were significantly higher ($P < 0.001$, ANOVA) at 30 and 60 min when subjects received Humalog® as compared with human soluble insulin. Humalog® antibody levels after up to 5.4 years of receiving Humalog® insulin were not elevated beyond the values at 1 year.

Conclusions We conclude that Humalog® insulin is effective in lowering postprandial glucose excursions even after up to 5.4 years of treatment.

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Keywords insulin lispro – Humalog®, long-term efficacy, post-prandial glucose excursions, Type 1 diabetes mellitus

Abbreviations DM, diabetes mellitus; HbA_{1c}, glycosylated haemoglobin; RIA, radioimmunoassay; kCal, kilocalories

Introduction

Improved glucose control is now recognized to reduce the long-term complications of diabetes [1,2]. Human soluble insulin as a short-acting insulin has the disadvantage that the onset of activity after subcutaneous injection is delayed by 30–90 min which often results in high postprandial glucose values [3,4]. Humalog® (Lys[B28], Pro[B29] insulin; Humalog®, Eli Lilly and Company, Indianapolis, IN) is a genetically engineered analogue of human insulin [5]. The altered amino acid sequence results in 'monomeric' properties of insulin action with more rapid absorption and onset of activity [6,7] and a more rapid peak effect [8,9] resulting in a lower postprandial glucose excursion in comparison to soluble insulin whether given preprandially [10,11] or postprandially [12]. A previous report indicated a slight increase in glucose levels towards the end of 1 year of Humalog® therapy [11]. The aim of this study was to evaluate the serum insulin and antibody levels and the efficacy of Humalog® in decreasing postprandial glucose excursions amongst those who had used the new insulin for at least 1 year.

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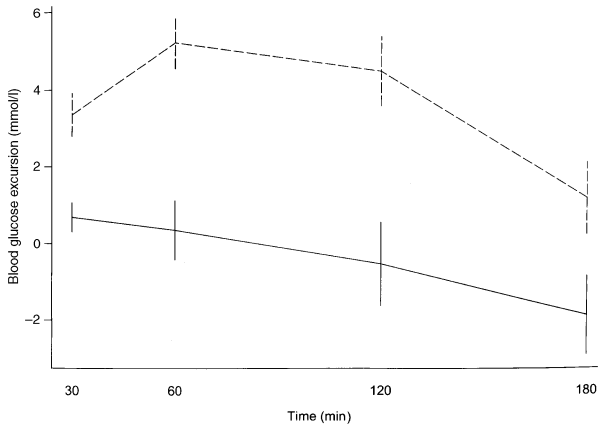

Figure 1 The mean (± SEM) postprandial glucose excursions after 20 subjects received either human soluble or Humalog® insulins on separate days. The glucose excursions were significantly lower ($P < 0.001$, ANOVA) after Humalog® (——) insulin compared to human soluble (- - - -) insulin at all three time periods.

Patients and methods

This was a double-blind, randomized crossover study conducted in 20 young patients (10 males and 10 females) with Type 1 DM attending a specialized diabetes centre. The mean (± SD) age at the first visit was 27.5 ± 5.3 years (range of 18–41 years) with a mean (± SD) duration of diabetes of 12.9 ± 7.3 years (range of 1.4–20 years). All subjects had used Humalog® as their short-acting insulin for at least 1 year (mean ± SD, 1.8 ± 1.6 years, range of 1.0–5.4 years), with NPH (11 subjects) or Ultralente (nine subjects) as their long acting insulins given twice daily. Mean HbA_{1c} at the first visit was 7.4 ± 2.0%. Four subjects had used Humalog® for at least 4 years. There were no other exclusion criteria.

All subjects reported in a fasting state (nothing to eat after 10:00 PM) on two separate mornings between 8:00 and 9:00 AM. Three subjects had to reschedule because of having hypoglycaemia on the morning of the study (two in the Humalog® group and one in the human soluble insulin group), but all subjects were restudied between 3 and 14 days of the initial test. The insulin dose was determined by patient interview as the mean over the previous three mornings and the caloric amount of their usual breakfast. The insulin dose (mean ± SD 8.5 ± 3.0 units) and calories consumed were kept the same for both meals and the dose was given 10 min prior to breakfast. The morning-long acting insulin was not given until after the test was completed. All subjects were asked to refrain from smoking and avoid any excitement or exercise during the 3-hour study period. They were allowed to read. Blood was drawn at 0 (fasting), 30, 60, 120 and 180 min after eating the meal, to test for blood glucose and insulin levels. The postprandial glucose excursions were calculated by subtracting the fasting glucose value from the 30-min and the 1, 2 and 3-hour postprandial glucose values. Two subjects had hypoglycaemic blood glucose values (< 2.22 mmol/l) in the Humalog® treated group during the testing.

The blood glucose values were determined the same day by a glucose oxidase method at Labcorp Lab (Englewood, CO) using an Olympus AU5000 (Olympus Inc., Tokyo, Japan) autoanalyser. The HbA_{1c} values, serum-free insulin levels, insulin antibody and cross-reactive antibody levels were determined using methods previously described [11,13].

Statistical methods

For the outcome insulin, and for each time-point, a repeated measures ANOVA with effects, period, order of treatment and their interaction, was employed. For the outcome glucose, for each time point, except baseline time, a repeated measures ANOVA with effects, period, order of treatment and their interaction, as well as the covariate, fasting blood glucose, was employed [14]. The insulin antibody data are presented as median (interquartile range).

Results

There was no evidence of a carry-over effect for either outcomes, blood glucose excursion or serum insulin values. Mean ± SD fasting blood glucose values were significantly higher in the Humalog® treated group (11.60 ± 5.16 mmol/l) as compared to 8.22 ± 4.01 mmol/l when human soluble insulin was used. Therefore, fasting blood glucose was included as a covariate in the analysis of blood glucose excursions at 30, 60, 120 and 180 min. Postprandial blood glucose excursions (Fig. 1) after receiving Humalog® were significantly lower compared to glucose excursions after receiving human soluble insulin ($P < 0.001$, ANOVA for 30, 60 and 120 min and $P < 0.05$, ANOVA for 180 min, Table 1). Estimated (least square means) glucose excursions data are given in the Table 1.

There were no differences ($P > 0.05$, *t*-test) in the fasting insulin levels when the subjects received human soluble insulin or Humalog®. The serum insulin levels at 30 and 60 min were significantly higher ($P < 0.001$, ANOVA, Table 1) after Humalog® as compared to the human soluble insulin (Fig. 2). The serum insulin levels were similar ($P > 0.05$, ANOVA, Table 1) at 120 min. At 180 min the serum insulin levels were higher ($P < 0.05$, ANOVA) after human soluble insulin compared to Humalog®.

The median human soluble insulin antibody levels were 0.65% (0.58–1.05%). The median Humalog® and cross-reactive antibody levels were 0.35% (0.08–0.7%) and 6.15% (3.13–14.08%), respectively.

Discussion

This study documents the effectiveness of Humalog® as compared to human soluble insulin in decreasing postprandial glucose excursions even after patients had used the new insulin for a mean of 1.8 years. A multicentre study suggested a slight

Table 1 Fasting and postprandial glucose excursions and serum insulin levels in the 20 subjects after receiving either Humalog® or human soluble insulin

	Mean ± SD blood glucose excursions (mmol/l)		Estimated glucose excursions Ψ* (mmol/l)			Mean ± SD insulin levels (pmol/l)	
	Human soluble	Humalog®	Human soluble		Humalog®	Human soluble	Humalog®
Fasting						3.0 ±0.13 *	3.24 ± 1.33
0.5 h postprandial	3.35 ± 2.51Ψ	0.68 ± 1.69	3.07	(0.62)	0.96	4.62 ± 1.57Ψ	8.46 ± 4.03
1 h postprandial	5.19 ± 2.98Ψ	0.34 ± 3.43	4.60	(0.42)	0.94	4.98 ± 1.90Ψ	7.50 ± 3.82
2 h postprandial	4.47 ± 4.01Ψ	−0.53 ± 4.84	3.78	(0.62)	0.16	5.22 ± 2.02*	5.64 ± 3.35
3 h postprandial	1.19 ± 4.20 **	−1.87 ± 4.60	0.43	(0.85)	−1.10	4.44 ± 1.90**	3.96 ± 1.57

The numbers given in parenthesis represent the common standard error using ANCOVA. * $P > 0.05$, ANOVA. ** $P < 0.05$, ANOVA. Ψ* $P < 0.001$, ANOVA. Ψ* Estimated glucose excursions were significantly lower at 30 min, 1 and 2 h ($P < 0.001$, ANCOVA) after Humalog® treatment but not different at 3 h ($P > 0.10$, ANCOVA).

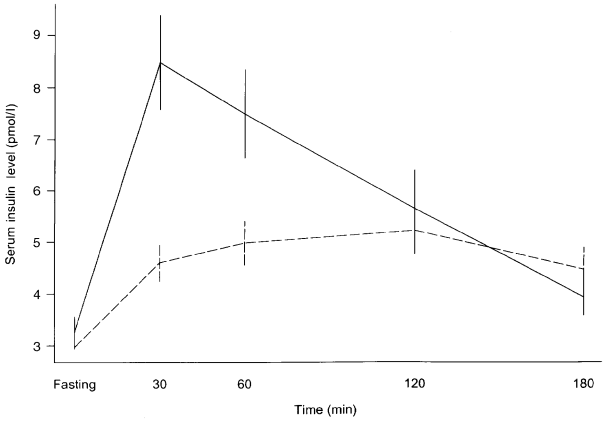

Figure 2 Mean (± SEM) serum insulin levels for 20 subjects after receiving either human soluble or Humalog® insulins on separate days. Levels were significantly higher ($P < 0.001$; ANOVA) at 30 and 60 min after receiving Humalog® (———) insulin in comparison to human soluble (- - - -) insulin. In contrast, at 3 h serum insulin levels were significantly higher when subjects received human soluble insulin ($P < 0.05$; ANOVA).

increase in blood glucose values at the end of the study period of 1 year [11]. This led to a concern of the possible loss of effectiveness of Humalog® when used for a longer time. We participated in the above multicentre study in 1992, with 39 subjects from our centre taking part in the study [10]. Since many of the subjects liked Humalog®, primarily because they could take the short-acting insulin just before eating, they went on to take part in the extension protocol. Thus, we had subjects who participated in this study who had used Humalog® for over 5 years. Fasting blood glucose values were significantly higher when Humalog® was given and this could have contributed to a greater drop in post meal glucose excursions.

Serum insulin levels were significantly higher at 30 and 60 min after the injection of Humalog® insulin compared to human soluble insulin. The rapid rise in serum insulin values was clearly reflected in the lower postprandial glucose excursions. The mixing of Humalog® and of human soluble insulins, as recently suggested [15], will allow therapy over a longer period of time when this is needed.

In the present study, the insulin antibody levels were similar to the previously reported antibody values at the end of 6 and 12 months of Humalog® treatment [11,13].

We conclude that the continued use of Humalog® insulin is effective in lowering postprandial glucose excursions with significantly higher insulin levels at 30 and 60 min after injection of Humalog®.

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References

1 The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–986.

2 Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D. Glucose control and the renal and retinal complications of insulin-dependent diabetes. *J Am Med Assoc* 1989; **261:** 1155–1160.

3 Bhaskar R, Chou MCY, Field JB. Time-action characteristics of Human soluble and NPH insulin in insulin-treated diabetics. *J Clin Endocrinol Metab* 1980; **50:** 475–479.

4 Gardner DF, Arakaki RF, Podet EJ, Nell LJ, Thomas JW, Field JB. The pharmacokinetics of subcutaneous human soluble insulin in type 1 diabetic patients: assessment using a glucose clamp technique. *J Clin Endocrinol Metab* 1986; **63:** 689–694.

5 Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28)-Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 1994; **43:** 396–402.

6 Howey DC, Bowsher RR, Brunelle RL, Rowe HM, Santa PF, Downing-Shelton J *et al.* [Lys(B28), Pro(B29)]-human insulin: effect

of injection time on post-prandial glycaemia. *Clin Pharmacol Ther* 1995; **58:** 459–469.
7 Galloway JA, Chance RE. *Diabetes Annual #8: Approaches to Insulin Analogues*. Amsterdam: Elsevier Science Publishers, 1994; 277–297.
8 Torlone E, Fanelli C, Rambotti AM, Kassi G, Modarelli F, DiVincenzo A *et al*. Pharmacokinetics, pharmacodynamics, and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys (B28), Pro(B29)] in IDDM. *Diabetologia* 1994; **37:** 713–720.
9 Brems DN, Brown PL, Bryant C, Chance RE, Green LK, Long HB *et al*. Altering the association properties of insulin by amino acid replacement. *Protein Eng* 1992; **5:** 527–533.
10 Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK *et al*. Pre-meal insulin analogue insulin-lispro vs. Humulin® R insulin treatment in young subjects with Type 1 diabetes. *Diabetic Med* 1996; **13:** 47–52.
11 Anderson JH, Brunelle RL, Koivisto VA, Pfitzner A, Trautmann ME, Vignati L *et al*. The Multicenter Insulin Lispro Study Group: Reduction of post-prandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 1997; **46:** 265–270.
12 Rutledge KS, Chase HP, Klingensmith GJ, Walravens PA, Slover RH, Garg SK. Effectiveness of post-prandial Humalog® in toddlers with diabetes. *Pediatrics* 1997; **100:** 968–972.
13 Fineberg NS, Fineberg SE, Anderson JH, Birkett MA, Gibson RG, Hufferd S. Immunologic effects of insulin lispro [Lys(B28), Pro(B29) human insulin] in IDDM and NIDDM patients previously treated with insulin. *Diabetes* 1996; **45:** 1750–1754.
14 ProcGLM, SAS System 6 12 for Windows. Cary, NC: SAS Institute, Inc., 1996.
15 Chase HP, Garg SK. At the controls: Lispro. *Diabetes Forecast* 1997; **35:** 32–39.