

# Lispro insulin for the treatment of severe subcutaneous insulin resistance

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## Abstract

**Objective** – To evaluate the clinical usefulness of the short-acting insulin analogue lispro in continuous subcutaneous insulin infusion (CSII) in type 1 patients with brittle diabetes due to severe subcutaneous insulin resistance who would otherwise require treatment with alternative insulin delivery systems (eg. by intraperitoneal insulin pump) necessary to prevent recurrent diabetic ketoacidosis.

**Research design and methods** – We proceeded in three patients with severe subcutaneous insulin resistance with a subcutaneous bolus test comparing the effects on plasma insulin levels and glycaemia of 15-30 U of regular insulin versus the same amount of lispro insulin. The successful bolus test prompted us to use lispro insulin in CSII in these patients. Adaptation of the insulin dose was made on the basis of daily capillary blood glucose measurements.

**Results** – In all patients lispro insulin was started in CSII (H-tron pump at 44 U/day) initially resulting in an improved metabolic control as reflected by acceptable blood glucose levels and by the HbA1c levels that dropped from 11 +/- 1% before to 7.9 +/- 1% during lispro treatment. During the following 8 weeks a progressive rise in blood glucose levels and rise in HbA1c levels to 10.3 +/- 0.1% was seen with consequently insulin dose adjustment to more than 500 U/day. Finally in all patients further insulin delivery by an intraperitoneal pump was required.

**Conclusions** – In three patients with subcutaneous insulin resistance the administration of subcutaneous lispro insulin resulted in acceptable metabolic control, but progressively all three patients developed a resistance syndrome against subcutaneous lispro insulin completely comparable to the resistance syndrome against subcutaneous regular insulin. Subcutaneous treatment with the insulin analogue therefore seems to overcome the problem of insulin resistance only temporarily.

**Key words:** *Insulin analogue lispro - subcutaneous insulin resistance - brittle diabetes*

## Introduction

The syndrome of subcutaneous insulin resistance is based on the concept that

the skin by some still elusive mechanism prevents or delays the absorption of insulin into the circulation (eg. by degradation) resulting in a severely unstable or brittle diabetes.<sup>1</sup> Clinically relevant subcutaneous insulin resistance is a rare but severe complication in type 1 diabetic patients that are often compelled to intramuscular or intravenous insulin administration or the use of implantable insulin pumps with

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intraperitoneal insulin delivery to prevent diabetic ketoacidosis.<sup>2-3</sup> Henrichs *et al* presented a new option in the treatment of the rare but frustrating condition of resistance to exogenous insulin by using a short-acting insulin analogue lispro (Humalog<sup>o</sup>, Eli Lilly) by continuous subcutaneous insulin infusion (CSII).<sup>4</sup> In normal conditions this rapid-acting insulin analogue offers most diabetics additional advantages to regular human insulin by generating higher plasma insulin levels at an earlier point in time and improvement of postprandial glycaemic control without increasing the risk of hypoglycaemia.<sup>5</sup> With this background the aim of this trial was to employ lispro insulin in a test bolus and later on as continuous subcutaneous treatment in three patients with subcutaneous insulin resistance and brittle diabetes who were otherwise forced to treatment with intravenous or intraperitoneal insulin pumps.

## Research design and methods

### A. Patient characteristics

Patient characteristics are described in Table 1. All three patients had a long existing history of type 1 diabetes with an initial period 2 to 8 years of acceptable glycaemic control with subcutaneous insulin administration.

**Table 1:** Patient characteristics

	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Female
Age (y)	29	30	34
Diabetes duration (y)	15	20	5
Resistance duration	8	8	2
BMI (kg/m <sup>2</sup> )	28	25	20
Mean Hb A1c (%)	12.3	10.6	10.1
DM Complications	Retinopathy Gastroparesis	Neuropathy Necrobiosis Lipoidica	Neuropathy Necrobiosis Lipoidica
Pump Complications	Pocket infection	Catheter obstruction Hypoglycaemic coma	Pocket infection Skin perforation

They all finally developed a syndrome of resistance to subcutaneous insulin leading to persistent hyperglycaemia in spite of more than 700 U of regular insulin in CSII per day. Due to this condition the patients spent more than 150 to 300 days a year in hospital necessitating the implantation of an insulin pump with intraperitoneal insulin administration (Minimed or Infusaid). This treatment resulted in good blood glucose control and managed to keep patients out of the hospital for longer periods. However all these patients developed pump-related complications such as intermittent catheter obstruction and associated severe hypoglycaemic attacks, pocket infection and perforation of the insulin pump through the abdominal wall. These complications necessitated explantation of the IP pump in two patients and the shut-down of the pump in one patient confining them back to IV insulin administration and chronic hospitalisation. At the time of the test bolus and during CSII with lispro, no signs of systemic infection were present.

### B. Detailed methods

We proceeded in these patients with a subcutaneous bolus test comparing the effects on plasma insulin levels and glycaemia of 15-30 U of regular insulin versus the same amount of lispro insulin. Bolus tests were performed at 8 am in

resting and fasting patients on different days, one hour after discontinuation of the overnight IV insulin. Glycaemia was monitored every 15-30 minutes by fingerprick capillary measurements (Glucocard, Menarini, Firenze, Italy). At the same time a venous sample for insulin determination by RIA assay (Biosource, Fleurus, Belgium) was taken. Upon relapse into hyperglycaemia (more than 500 mg/dl) or at least three hours after the bolus, the IV insulin pump was restarted and meals were given.

The successful bolus test prompted us to use lispro insulin in CSII in these patients. CSII was administrated using H-tron V-100 pumps (Disetronic, Brugdorf, Switzerland) if needed allowing for 24 different rythms. Daily capillary blood glucose monitoring (4 times a day) was performed by patients using Glucocard. The patients were allowed to return to their homes after 5 days. They were asked to adapt their insulin dose on the basis of glucose monitoring measurements after phone contact with our centre. HbA1c (%) was measured at the start, 3 weeks after lispro start and at the end of the trial using an HPLC method (normal levels 3.6 - 6.4 %) as were insulin antibodies using a RIA method (in house assay).

## Results

### A. Bolus test with regular insulin versus lispro insulin

In all patients the subcutaneous administration of 15 or 30 U of lispro insulin resulted in a clear decrease in blood glucose, even resulting in hypoglycaemia in the patient receiving 30 U (Figure 1A). This effect on blood glucose was mirrored by a clear rise in plasma insulin levels in all patients. Administration of a similar amount of

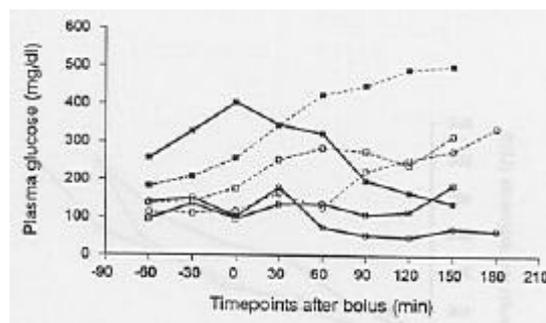


Figure 1A- Bolus test evaluating plasma glucose levels.

Plasma glucose levels are represented after 15 or 30 U of regular (dotted line) or lispro (full line) subcutaneous insulin administration. In all patients the administration of lispro resulted in a clear decrease in blood glucose even resulting in hypoglycaemia in the patient receiving 30U (patient O). On the contrary, administration of regular insulin could not maintain normoglycaemia and even resulted in severe hyperglycaemia and ketosis in one patient (■).

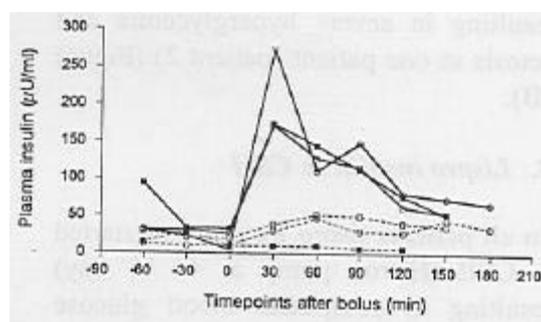


Figure 1B –Bolus test evaluating plasma insulin levels

Plasma insulin levels are represented after 15 or 30 U of regular (dotted line) or lispro (full line) subcutaneous insulin administration. This resulted in a marginal increase in plasma insulin levels after regular insulin administration in two patients (□ and O) or no increase at all in one patient (●). On the contrary, there was a clear rise in plasma insulin levels after lispro insulin in all patients.

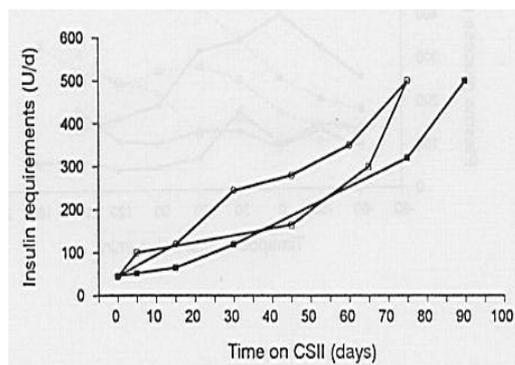


Figure 2 – Lispro requirements during CSII  
Daily capillary blood glucose monitoring (four times a day) was performed by patients using Glucocard. The patients were allowed to return to their homes after 5 days. They were asked to adapt their insulin dose on the basis of glucose measurements after phone contact with our centre (patient O, patient ■ and patient ●).

regular insulin only resulted in a marginal increase or no increase at all in plasma insulin levels and could not maintain normoglycaemia, even resulting in severe hyperglycemia and ketosis in one patient (patient 2) (Figure 1B).

### B. Lispro insulin in CSII

In all patients lispro insulin was started in CSII (H-tron pump at 44 U/ day) resulting in acceptable blood glucose levels (60-300 mg/dl) without ketoacidosis. In the patient where the intraperitoneal pump was left inside, the pump was shut off (patient 2). During the following weeks patients lived a normal life out of the hospital but a progressive rise in blood glucose levels was seen and consequently the Lispro insulin dose was adjusted to more than 500 U/day (Figure 2). During the period on lispro insulin metabolic control initially improved as reflected by HbA1c

levels that dropped from 11 +/- 1% before to 7.9 +/- 1% during lispro treatment. All patients were treated for at least 8 weeks with subcutaneous lispro insulin. Progressively all three patients developed a resistance syndrome against subcutaneous lispro insulin comparable to the resistance syndrome against subcutaneous regular insulin resulting in ketoacidosis in one patient (patient 2). This recurrence of resistance was reflected by a rise in HbA1c to 10.3 +/- 0.1% despite the administration of more than 500 U lispro per day. The resistance was not caused by formation of insulin antibodies in plasma since very low levels were measured in all patients both before and after lispro treatment (1% versus 1% in all patients).

### Discussion

Subcutaneous insulin resistance is a rare but severe condition of which the aetiology is still unknown.<sup>1</sup> Enzymatic subcutaneous defects and antibody formation have been implicated, but due to the low incidence of the defect, clinical investigation is difficult. In many cases a pseudo-resistance is present with psychological or psychiatric disturbances and patient manipulation as the cause.<sup>2</sup> Our university clinic has a population of about 1000 type 1 diabetic patients with 5 patients presenting with the syndrome of subcutaneous insulin resistance. In the 3 patients studied in the present trial, all manipulation was excluded and the diagnosis of idiopathic subcutaneous insulin resistance was made.

Treatment alternatives for patients with subcutaneous insulin resistance are few, confining them to hospital for chronic IV insulin administration or necessitating the implantation of an insulin pump with IP insulin delivery. Chronic IV insulin administration is undesirable since it is

expensive, disrupts the patient's life and carries a high risk of sepsis. Programmable pumps with intraperitoneal insulin delivery are again expensive, but an acceptable alternative treatment.<sup>2,3</sup> Unfortunately these pumps are not devoid of technical problems, so there is still a need for a better treatment for patients with subcutaneous insulin resistance.

Introduction of lispro insulin allowed our patients to be kept out of hospital and live a normal life for many weeks, but in all patients a recurrence of subcutaneous insulin resistance was observed. Initial observations by others<sup>4,5</sup> and the initial subcutaneous bolus test resulting in a spectacular metabolic effect, suggested that cross-resistance between lispro and regular insulin would not exist and subcutaneous lispro administration might be the solution for this group of patients. Although the underlying mechanism of subcutaneous insulin resistance is still unknown, it is most probably based on a process of local interference with insulin absorption finally resulting in slow and especially unreliable insulin absorption with unstable diabetes.<sup>5</sup> Whether the diminished local absorption of insulin is related to enzymatic degradation ( eg by a protease ) or to an immunological process (antibody related) remains still elusive.<sup>6-8</sup> The greatly diminished tendency of lispro insulin to self-associate results in a more rapid insulin absorption<sup>9</sup> and could allow escape to the local insulin degradation process. On the other hand Lispro insulin seems not to differ dramatically immunologically from regular human insulin. The change in amino acid order of lispro might even be responsible for the increased immunogenicity of this type of insulin.<sup>10-12</sup>

In contrast to observations made

previously by others,<sup>4,13,14</sup> we saw, after an initial period of good metabolic control, a recurrence of the subcutaneous resistance under lispro treatment. The clinical features of the resistance syndrome were identical to the resistance to regular insulin and resistance was not based on the formation of insulin antibodies.

In conclusion, we noticed that in these three cases of resistance against subcutaneous regular insulin, introduction of lispro insulin resulted in good metabolic control for only a short period. However clinically disappointing, this observation may be a stimulus for the further study of the mechanisms underlying the syndrome of subcutaneous insulin resistance and eventually lead to new therapeutic options for this group of patients.

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