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# Intramuscular injection of insulin lispro or soluble human insulin: pharmacokinetics and glucodynamics in Type 2 diabetes

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## Abstract

**Aim** The aim of the study was to compare the pharmacokinetics and glucodynamics of insulin lispro and soluble human insulin following intramuscular (i.m.) injection in patients with Type 2 diabetes with secondary failure of sulphonylureas.

**Methods** Single 15-U i.m. doses of insulin lispro or soluble human insulin were administered to 16 patients in a two-way, randomized, crossover design. Glucodynamic and pharmacokinetic parameters were determined over 6 h after insulin injection using clamp techniques.

**Results** Insulin $C_{max}$ was significantly higher (971 ± 217 vs. 659 ± 141 pmol/l, $P < 0.001$) and $T_{max}$ was significantly shorter (46.9 ± 27 vs. 94.7 ± 50.1 min, $P = 0.002$) with insulin lispro. Glucose infusion rate (GIR) curves showed clear separation 20 min after injection and were significantly greater for insulin lispro during the 40–60, 60–80 and 80–100-minute time intervals. Total glucose infused was only approximately 5% larger with insulin lispro during the 6-h follow-up, due to lower insulinaemia at later time points. The glucose $R_{max}$ and $TR_{max}$ were not statistically different between insulin treatments.

**Conclusion** This study shows that i.m. injection of insulin lispro is followed by its more rapid absorption, which results in stronger metabolic effect in the first 2 h when compared with soluble human insulin under the same test conditions.

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**Keywords** insulin lispro, intramuscular injection, pharmacokinetic, glucodynamic

## Introduction

Insulin lispro is a newly developed analogue of human insulin with a much faster rate of absorption from the subcutaneous (s.c.) site and a significantly quicker time to peak activity when compared with soluble human insulin [1]. The pharmacokinetic (PK) characteristics of insulin lispro more closely mimic normal early insulin response to a meal than soluble human insulin [2,3]. This early-phase insulin secretion normally occurs several minutes after the start of food intake [4] and is reduced or absent in most patients with Type 2 diabetes [5]. Deterioration of the early-phase insulin response is a major factor in the worsening of post-prandial blood glucose levels and progression of Type 2 diabetes [6]. Evidence has

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accumulated that post-prandial hyperglycaemia as a fraction of total hyperglycaemia is an independent risk factor for cardiovascular complications and death [7–9]. Treatment with soluble human insulin, which peaks approximately 2–3 h after s.c. injection, results in insufficient insulinaemia during the early post-prandial phase and hyperinsulinaemia in the late post-prandial phase [10].

A change in route of administration of various insulins needs investigating because (i) daily changes of the site of injection may significantly affect blood glucose regulation on a day-to-day basis, and (ii) different insulin formulations may show different PK and pharmacodynamic (PD) characteristics when injection site is changed. I.m. injection commonly occurs in lean patients [11,12]. Additionally, in some cases i.m. insulin infusion may be a better choice than s.c. insulin infusion when insulin pumps are used [13]. It has been suggested that absorption of soluble human insulin is faster from i.m. than from s.c. sites, while this difference has not been observed with insulin lispro [14,15]. This may indicate that soluble human insulin given i.m. had an absorption curve similar (although not identical) to insulin lispro given either i.m. or s.c. [16,17]. Implicitly, it suggests that i.m. injection of soluble human insulin would improve its PK (closer to physiologic curves) and mimic the PK and metabolic effects of s.c. insulin lispro.

The objectives of this study were to compare the PK of the two insulin preparations after administration by the i.m. route and to assess whether potential differences between the two insulins translate into different glucodynamic effects in the post-injection period in patients with Type 2 diabetes who display signs of secondary failure to sulphonylureas.

## Materials and methods

### Patients

Sixteen non-obese (body mass index (BMI) < 25 kg/m$^2$) patients with Type 2 diabetes mellitus participated in the study. Only patients who presented with secondary failure of oral hypoglycaemic agents (defined as an $HbA_{1c} > 7.5\%$ despite treatment with maximal doses of glibenclamide) were included in the study. Patients were excluded if they had an $HbA_{1c} \geqslant 14\%$, severe complications of diabetes, other significant diseases or insulin allergy.

### Study design

The study used an open-label, randomized, two-way crossover design and the protocol was approved by the Vuk Vrhovac University Ethical Review Board. At visit 1, after signing informed consent, patients were examined and inclusion and exclusion criteria were assessed. Eligible patients were randomized and scheduled for the first clamp test, which has been described in detail elsewhere [18]. They were hospitalized the day before the clamp and received their normal dose of glibenclamide at 6.00 p.m. All patients were fasted overnight and remained fasted during the clamp procedures that were carried out with a Biostator® (Life Science Instruments, Elkhart, IN, USA) starting the next morning at 6.30 a.m. A dorsal vein of the left hand was cannulated in retrograde direction with a double lumen catheter connected to the glucose sensor of the Biostator. This hand was then placed in a thermoregulated wooden box at a temperature of 63°C. Baseline insulin was infused at 0.20 mU/kg per min by means of a high precision peristaltic pump. Blood glucose was clamped at 6.7 mmol/l; coefficient of variation 0–360 min ($CV_{0–360min}$) for blood glucose values after injection of soluble insulin was 4.69% and $CV_{0–120min}$ was 5.02%, while $CV_{0–360min}$ after insulin lispro was 5.20% and $CV_{0–120min}$ was 5.89%.

After a baseline period of 90 min, at time 0 patients were given an i.m. dose of 15 U of either insulin lispro (Humalog®; Eli Lilly and Co., Indianapolis, IN, USA) or soluble human insulin (Humulin R®; Eli Lilly and Co.) according to the randomization scheme. The i.m. injection was administered in the gluteal region by study personnel with assistance from an experienced specialist in the field of ultrasound diagnostics. Prior to the start of the study, the thickness of the subcutaneous fat layer in this region was measured by ultrasound for each patient. Intramuscular administration of insulin was then assured by using sufficient length needles (0.9 × 44 mm) and by adjustment of the depth of injection.

For determination of plasma glucose and serum insulin concentrations, blood samples were collected at: –90, –10, 0, 10, 20, 30, 40, 50, 60, 80, 100, 120, 180, 240, 300 and 360 min. Plasma glucose was analysed with a Glucose Analyser® II™ (Beckman Instruments, Munich, Germany) and if glucose values were different from the Biostator, the latter was re-calibrated.

After the first study day, patients were treated for the following 2–4 days with their normal dose of oral hypoglycaemic agent and then returned to the clinic for the second study day. The clamp procedure was repeated as described above but the patient received the opposite insulin to that administered on the first study day.

### Measurements

$HbA_{1c}$ was determined by ion-exchange chromatography using an HPLC system and DCA2000 test (Bio-Corporation, Elkhart, IN, USA; normal range 4.2–6.2%) [19]. Serum insulin concentrations were measured by means of a radioimmunoassay (Insulin Coat-a-Count kit; Diagnostic Products, Los Angeles, CA, USA) using a particular antibody TIN 183. This method gives equivalent analytical responses for human insulin and insulin lispro and has been validated in detail previously [20]. The lower limit of quantification was 43 pmol/l with an interassay CV of 18%; at the level of 345 pmol/l and higher, the interassay CV was < 6%.

### Calculations and statistical analysis

The serum concentrations of immunoreactive insulin were used to determine PK variables including maximum insulin

concentration ($C_{max}$), time to maximum concentration ($T_{max}$) and total area under the concentration–time curve ($AUC_{insulin0–360}$).

An average value of all blood glucose measurements within each 10-min interval, beginning with the time point –90 min, was calculated for the full period of 450 min of both clamp procedures. Additionally, an average of all glucose infusion rate (GIR) values within each 10-min interval was calculated and used in further statistical analysis. The GIR values were used to determine glucodynamic variables including maximum infusion rate ($R_{max}$) and time to maximum infusion rate ($TR_{max}$), as well as area under the curve of infusion rate vs. time ($AUC_{glucose0–360}$).

An analysis of variance model, incorporating effects for sequence, period and treatment, was used to evaluate the primary PK and glucodynamic variables. Due to some missing observations, least-square means were generated and tests for significance in separation of least-square means were performed. Incremental amounts of infused glucose were determined, in increments of 20 min for the first 4 h after injection of the insulin and then in 30-min increments for the last 2 h of the glucose clamp. Significance tests for the least-square treatment means were performed for each time interval. Statistical calculations were carried out with the SAS system, version 6.12 (SAS Institute, Cary, NC, USA).

## Results

### Patients characteristics

The mean (± SD) age of the patients was 56 ± 5 years (range 45–64 years), the duration of diabetes was 8 ± 4 years (range 1–17 years) and the mean dose of glibenclamide was 19 ± 2 mg/day. The mean baseline $HbA_{1c}$ level was 9.8 ± 1.6% and the mean BMI was 24.5 ± 0.4 kg/m$^2$.

### Insulin pharmacokinetics

The serum insulin concentration (mean ± SEM) during the clamp test is shown in Fig. 1a and the PK variables are summarized in Table 1. Mean serum insulin concentration was not different between two treatments at the start of the baseline period (102 ± 79 pmol/l for insulin lispro vs. 78 ± 37 pmol/l for soluble insulin) and immediately before the injection (112 ± 60 pmol/l for insulin lispro vs. 148 ± 84 pmol/l for soluble insulin). Following i.m. injection, the mean $C_{max}$ was significantly greater for insulin lispro compared with soluble human insulin (971 ± 217 vs. 659 ± 141 pmol/l; $P < 0.001$). The mean $T_{max}$ was significantly shorter for insulin lispro compared with soluble human insulin (46.9 ± 27.0 vs. 94.7 ± 50.1 min, $P = 0.002$). Consequently, the insulin levels achieved between the 20th and 100th minutes after injection of insulin lispro were significantly higher than after soluble human insulin ($P < 0.001$). After this time period, no difference between the two insulins was observed except for a higher serum insulin at 240 min ($P = 0.026$) and 300 min ($P = 0.006$) with soluble human insulin. The $AUC_{insulin0–360}$ was approximately 3% greater after insulin lispro compared with soluble human insulin, but the difference was not statistically significant.

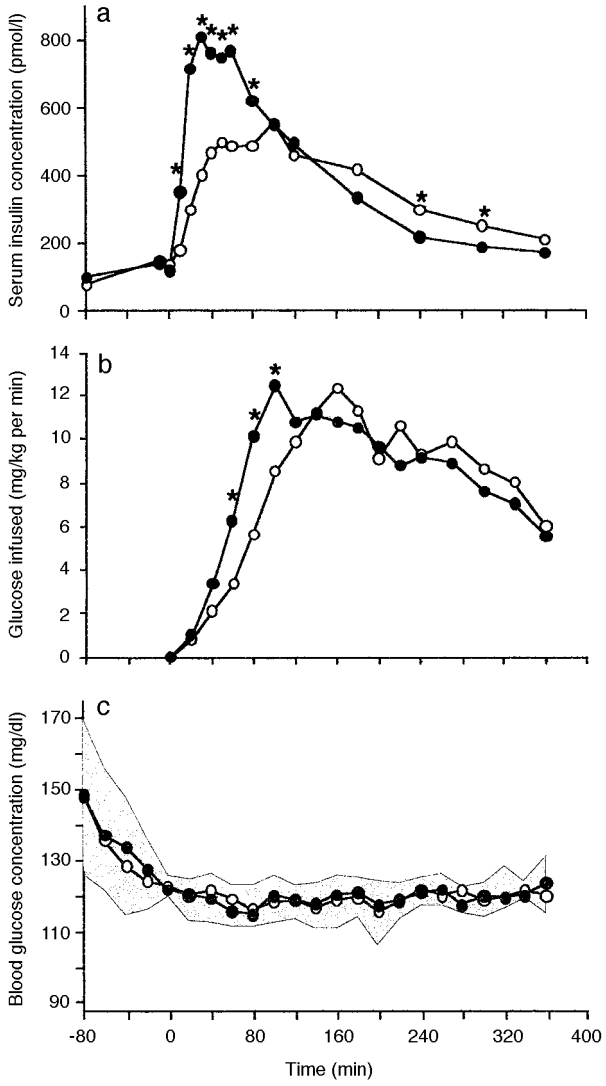


**Figure 1** (a) Serum immunoreactive insulin concentrations, (b) average glucose infusion rates in each 10-min time interval, and (c) blood glucose concentrations during the clamp, in 16 patients with Type 2 diabetes following intramuscular injection of either insulin lispro (●) or soluble human insulin (○) at time 0. For (a) and (b) the mean values are shown with statistical significance as $*P < 0.01$ insulin lispro vs. soluble human insulin, and for (c) mean values are shown with SD for insulin lispro above the line and for regular human insulin below the line.

### Insulin pharmacodynamics

Sequential calculation of GIR revealed a faster increase of glucose consumption after i.m. insulin lispro during the

**Table 1** Insulin pharmacokinetic and glucodynamic parameters determined after intramuscular injection of either insulin lispro or soluble human insulin during a euglycaemic clamp; values are mean ± SD ($n$ = 16)

| | Insulin lispro | Regular human insulin | $P$ |
|---|---|---|---|
| Insulin pharmacokinetics | | | |
| $C_{max}$ (pmol/l) | 971 ± 217 | 659 ± 141 | < 0.001 |
| $T_{max}$ (min) | 46.9 ± 27.0 | 94.7 ± 50.1 | 0.002 |
| AUC (pmol.h/l) | 2200 ± 398 | 2145 ± 397 | NS |
| Glucodynamic parameters | | | |
| $R_{max}$ (mg/min per kg) | 935.6 ± 264.2 | 879.8 ± 268.6 | NS |
| $TR_{max}$ (min) | 139.4 ± 55.2 | 141.3 ± 52.9 | NS |
| Total glucose infused (g/kg) | 134.7 ± 56.7 | 128.2 ± 56.1 | NS |

NS, Non-significant ($P$ > 0.05).

**Table 2** Calculated least-mean squares values for glucose infused (mg/kg per min) during each time period following intramuscular injection at time 0 of either insulin lispro or soluble human insulin ($n$ = 16)

| | Insulin lispro | Regular human insulin | $P$ |
|---|---|---|---|
| 20–40 min | 3.32 | 2.09 | 0.093 |
| 40–60 min | 6.23 | 3.34 | < 0.001 |
| 60–80 min | 10.17 | 5.58 | < 0.001 |
| 80–100 min | 12.47 | 8.51 | < 0.001 |
| 100–120 min | 10.79 | 9.91 | NS |
| 120–140 min | 11.13 | 11.23 | NS |
| 140–160 min | 10.79 | 12.36 | 0.032 |

NS, Non-significant ($P$ > 0.05).

first part of the clamp test, compared with i.m. soluble human insulin. GIR for each 20-min time interval in the period between 20 and 100 min clearly indicated a greater metabolic effect of insulin lispro during this period (Fig. 1b). The least-mean square values were significantly ($P$ < 0.001) greater for insulin lispro compared with soluble human insulin at the 40–60, 60–80 and 80–100 min intervals (Table 2). ANOVA revealed a significant ($P$ = 0.026) overall treatment effect. The GIR after insulin lispro was 69% higher in the first hour and 39.7% higher in the second hour than that observed after soluble human insulin. This difference disappeared at later time points, resulting in only a 5% increase in total amount of glucose infused during the 6-h clamp after administration of insulin lispro compared with soluble human insulin (insulin lispro, 134.7 ± 56.7 g/kg; regular human insulin, 128.2 ± 56.1 g/kg). The $R_{max}$ was higher with insulin lispro but the difference was not statistically significant and there was also no significant difference in $TR_{max}$.

## Discussion

This randomized, crossover study of 16 patients with Type 2 diabetes showed that insulin lispro resulted in an earlier and higher peak serum insulin compared with an equivalent dose of soluble human insulin when both insulins were given by the i.m. route. The observed differences in the pharmacodynamics with the two insulins indicated a stronger metabolic effect of insulin lispro in the first hours after administration.

After i.m. injection of each insulin, $C_{max}$ was higher and $T_{max}$ was shorter for insulin lispro than for soluble human insulin. As a consequence, the amount of glucose infused at earlier time points was greater for insulin lispro. It was anticipated that the $R_{max}$ would be higher and the $TR_{max}$ would be shorter for insulin lispro. In fact, $R_{max}$ was approximately 7% higher with insulin lispro but this difference was not significant. The lack of a difference in $R_{max}$ might be explained by peripheral tissue insensitivity to insulin action and the small number of patients in the trial. Relatively prolonged $TR_{max}$ for insulin lispro compared with previously published data was probably related to a 'plateau' phenomenon which was observed in several patients when given insulin lispro. In these individuals the first peak of glucose infusion occurred in the first 2 h and was followed by a second peak, with only a slight increase, observed much later (late second or beginning of the third hour). The phenomenon occurred less frequently when soluble human insulin was tested. The 'plateau' phenomenon explains the much stronger metabolic effect of lispro insulin in the beginning, despite similar $R_{max}$ and $TR_{max}$ to those obtained after soluble human insulin.

The most striking difference between the results of this study and results reported in healthy volunteers tested under similar conditions relates to the outcome of the comparative analysis of the PK curves of the two insulins [10,14]. In the study of healthy volunteers, $C_{max}$ and $AUC_{0–120\ min}$ were not different between insulin lispro i.m. or s.c. and soluble human insulin injected i.m., although the $T_{max}$ was longer for soluble human insulin injected i.m. [14]. However, these PK data were not in accord with the observation of the stronger metabolic activity of i.m. or. s.c. insulin lispro vs. i.m. soluble human insulin in the first hours after injection in healthy volunteers [14]. Our study confirms that the metabolic effect of soluble human insulin injected i.m. is weaker than that of insulin lispro injected by either the i.m. or s.c. route and is much closer to that of soluble human insulin given s.c.

Possible explanations for these differences may relate to (i) the different populations studied (healthy volunteers vs. patients with Type 2 diabetes), or (ii) location of the i.m. injection (right thigh in the previous trial; gluteal muscle with ultrasound guidance in this trial). The observed glucodynamic differences in the present study correlate with the higher insulin concentrations achieved in the first

hours after injection of insulin lispro compared with soluble human insulin. However, the similar results of a stronger initial glucodynamic effect of insulin lispro in the present study and the previous study suggest a possible explanation.

The post-prandial period in patients with Type 2 diabetes is characterized by insufficient early-phase insulin secretion after the food intake, resulting in post-prandial hyperglycaemia. Nolan *et al*. [21] have shown that patients with Type 2 diabetes also display a kinetic defect, which manifests as a slower response of the intracellular signalling cascade to insulin receptor binding in addition to decreased glucose uptake (insulin resistance). It is possible that these pathophysiological abnormalities may attenuate the metabolic effect of insulin lispro in these patients despite its more rapid absorption rate and higher insulinaemia in the early post-injection period. The results of this and other studies show that insulin lispro given s.c. or i.m. maintains its more potent metabolic effect in the early post-injection period compared with soluble insulin [2]. The preserved effectiveness of insulin lispro in patients with Type 2 diabetes mellitus might relate to reduced hepatic glucose output secondary to the suppressive action of the early and high peak of insulinaemia after insulin lispro, as shown in recent studies [2].

The observed metabolic effect of insulin lispro in the early post-injection period may have relevance in the treatment of Type 2 diabetes, since it correlates with the early post-prandial period. Several recent clinical and epidemiological trials emphasize the importance of post-prandial blood glucose levels as a risk factor for macro-vascular complications in patients with Type 2 diabetes [7–9]. It may be postulated that the appropriate use of insulins with improved PK and PD characteristics to intervene in the cycle of deficient early-phase insulin response, increased post-prandial glucose, glucotoxicity and further increases in post-prandial blood glucose could prevent or delay some of these dangerous outcomes of the disease. This hypothesis requires further evaluation in large-scale interventional clinical trials.

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