

# Comparison of Continuous Subcutaneous Insulin Infusion and Multiple Daily Injection Regimens Using Insulin Lispro in Type 1 Diabetic Patients on Intensified Treatment

## A randomized study

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**OBJECTIVE** — To compare the efficacy of 2 intensified insulin regimens, continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI), by using the short-acting insulin analog lispro in type 1 diabetic patients.

**RESEARCH DESIGN AND METHODS** — A total of 41 C-peptide–negative type 1 diabetic patients (age  $43.5 \pm 10.3$  years; 21 men and 20 women, BMI  $24.0 \pm 2.4$  kg/m<sup>2</sup>, diabetes duration  $20.0 \pm 11.3$  years) on intensified insulin therapy (MDI with regular insulin or lispro,  $n = 9$ ; CSII with regular insulin,  $n = 32$ ) were included in an open-label randomized crossover study comparing two 4-month periods of intensified insulin therapy with lispro: one period by MDI and the other by CSII. Blood glucose (BG) was monitored before and after each of the 3 meals each day.

**RESULTS** — The basal insulin regimen had to be optimized in 75% of the patients during the MDI period (mean number of NPH injections per day = 2.65). HbA<sub>1c</sub> values were lower when lispro was used in CSII than in MDI ( $7.89 \pm 0.77$  vs.  $8.24 \pm 0.77\%$ ,  $P < 0.001$ ). BG levels were lower with CSII ( $165 \pm 27$  vs.  $175 \pm 33$  mg/dl,  $P < 0.05$ ). The SD of all the BG values ( $73 \pm 15$  vs.  $82 \pm 18$  mg/dl,  $P < 0.01$ ) was lower with CSII. The frequency of hypoglycemic events, defined as BG levels  $< 60$  mg/dl, did not differ significantly between the 2 modalities (CSII  $3.9 \pm 4.2$  per 14 days vs. MDI  $4.3 \pm 3.9$  per 14 days). Mean insulin doses were significantly lower with CSII than with MDI ( $38.5 \pm 9.8$  vs.  $47.3 \pm 14.9$  U/day, respectively,  $P < 0.0001$ ).

**CONCLUSIONS** — When used with external pumps versus MDI, lispro provides better glycemic control and stability with much lower doses of insulin and does not increase the frequency of hypoglycemic episodes.

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According to the results of the Diabetes Control and Complications Trial (DCCT) (1), intensive diabetes management should be proposed for most type 1 diabetic patients to prevent long-term complications. However, the ideal insulin regimen should simultaneously achieve 2 goals: maintenance of near-euglycemia and avoidance of frequent and severe hypoglycemia.

Several studies have suggested that continuous subcutaneous insulin infusion (CSII) could provide better glycemic control (2–4) with a lower risk of hypoglycemia (5,6) than multiple daily injections (MDI). But very few of these studies were randomized, and all used regular insulin. We and others (7–9) also reported that, when used in external pumps, the short-acting insulin analog lispro provided better glycemic control than regular insulin without increasing the frequency of hypoglycemic episodes.

However, to the best of our knowledge, the benefits of lispro use in CSII and MDI have never been compared. Therefore, the aim of the present work was to compare the efficacy on glycemic control and hypoglycemia frequency of 2 new intensified insulin regimens, CSII and MDI, with insulin lispro in a randomized study.

**RESEARCH DESIGN AND METHODS** — The study protocol was approved by the Ethics Committee of Toulouse, and all of the patients gave written consent.

### Patients

A total of 41 type 1 diabetic patients between 21 and 65 years of age participated in the study. At enrollment, 32 were treated by CSII with regular insulin and 9 by MDI with regular insulin or insulin lispro. The inclusion criteria were HbA<sub>1c</sub>  $< 10.0\%$ , negative C-peptide, and experience of intensified

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**Abbreviations:** BG, blood glucose; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; MDI, multiple daily injections.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—Patient characteristics**

<i>n</i>	41
Sex (M/F)	21/20
Age (years)	43.5 ± 10.3 (21.0–65.4)
Weight (kg)	68.2 ± 10.0 (47–87)
BMI (kg/m <sup>2</sup> )	24.0 ± 2.4 (18.7–28.5)
Duration of diabetes (years)	20.0 ± 11.3 (4.0–42.0)
HbA <sub>1c</sub> (%)	8.39 ± 0.87 (6.8–10.0)
Daily insulin dose (U/day)	43.6 ± 13.5

Data are *n* or means ± SD (range).

insulin therapy. None of the patients had untreated retinopathy, impaired renal function, gastric neuropathy, BMI >30 kg/m<sup>2</sup>, daily insulin dose >2 U/kg, history of hypoglycemia unawareness, or any severe disease that could interfere with the study. Their characteristics are shown in Table 1.

### Study design

The study was conducted in a randomized crossover open-label design to compare 2 methods of intensified insulin therapy using insulin lispro (Humalog U-100; Lilly France, Saint-Cloud, France), CSII with a programmable external pump (MiniMed 506 or 507; Minimed, Sylmar, CA, and HTron D or V; Disetronic, Burgdorf, Switzerland), and MDI with an optimal dose of NPH (Fig. 1). Insulin lispro and NPH were injected separately at different sites using insulin pens. Regardless of their previous treatment, all of the patients were submitted to a 6-week run-in period of CSII treatment with regular insulin. The patients were randomly assigned to either CSII with lispro or MDI with 3 injections of lispro (before meals) and 2 injections of NPH (before breakfast and at bedtime) for a 4-month period (first period). They were then switched to the other treatment for another 4 months (second period). The patients were seen by the same investigator at the University Hospital of Toulouse at the end of each study period. During each period of treatment, the patients were seen by their usual diabetologist 2 and 8 weeks, respectively, after each change of insulin regimen to optimize their glycemic control. All of these diabetologists were members of the Study Group for the Development of Pump Therapy in Diabetes, which is composed of private practice diabetologists who follow a training course on pump therapy 3 times a year and work in collaboration with the University Hospital.

### Investigator and patient instructions

Daily capillary blood glucose (BG) measurements were performed before and 2 h after each meal and, in the event of hypoglycemic symptoms, using a Glucomatic Esprit memory meter (Bayer Diagnostic, Puteaux, France). The glycemic targets were 70–120 mg/dl before meals or during fasting periods and 120–180 mg/dl 2 h after meals. The insulin regimen was adjusted by the patient based on the results of self-monitoring and by the investigators at each visit. During the MDI period, the investigators were advised to add a third injection of NPH at noon if BG before dinner was not within the target range. To make this change as soon as necessary, the first visit was planned 2 weeks after the beginning of the MDI period. The patients were asked to check ketonuria twice a day, at morning and at bedtime, and in the event of hyperglycemia. They were instructed to record in a notebook all episodes of hypoglycemia and any technical or metabolic incident, such as ketonuria or severe hypoglycemia, as defined by the DCCT criteria.

### Data collection and biochemical determinations

During each period of treatment, a first visit was made 2 weeks after the change of treatment to optimize basal insulin replacement. Except for this visit, the frequency of the visits was normal (every 2 months). At each visit, insulin dose and adverse events were noted. At the end of each study period, blood samples were drawn for HbA<sub>1c</sub> determination, and the memory meters were downloaded on a computer

(WinGlucofacts software; Bayer Diagnostic) to obtain mean glycemia, the SD of BG, and the number of hypoglycemic events (defined by BG measurements <60 mg/dl) during the previous 14 days. Blood pressure and weight were also recorded. At the end of the study, the patients were asked to indicate if they preferred to keep using insulin lispro or to go back to regular insulin and to choose between the 2 types of insulin delivery (MDI or CSII).

### Assay methods

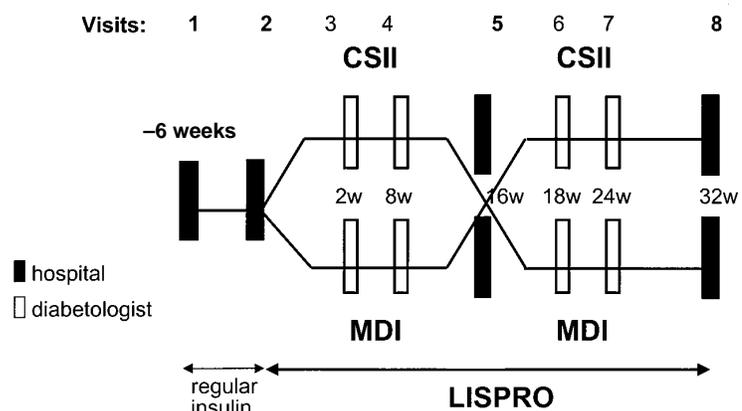
HbA<sub>1c</sub> was measured by high-performance liquid chromatography (normal range 4.0–6.0%) before randomization and at the end of each study period. All of the measurements were centralized.

### Statistical analysis

Calculations were performed with Statview (Abacus Concepts, Berkeley, CA). Results are given as means ± SD. All tests were 2-tailed, and *P* values <0.05 were considered statistically significant.

Changes in continuous criteria (efficacy criteria: HbA<sub>1c</sub>, mean glycemia, and SD of BG) were studied by analysis of variance applied to crossover study with period, treatment group, and interaction factors. Categorical criteria (adverse events) were compared by the  $\chi^2$  test.

**RESULTS** — Among the 41 patients enrolled, 40 completed the study. One subject dropped out 3 weeks after the beginning of the first period of treatment, which was MDI in his case. Before enrollment, this patient was on CSII, and he could not tolerate the difficulties encountered with the MDI regimen.



**Figure 1**—Randomized crossover open-label design comparing 2 methods of intensified insulin therapy (CSII and MDI) using insulin lispro.

All of the results could be analyzed during the 2 periods of treatment, because no carryover effect was observed.

**Clinical results**

We observed no significant difference in weight (CSII 68.7 ± 10.0 kg vs. MDI 69.0 ± 9.5 kg) and systolic (CSII 133.5 ± 15.1 mmHg vs. MDI 134.4 ± 13.9 mmHg) or diastolic (CSII 77.2 ± 9.3 mmHg vs. MDI 78.6 ± 9.5 mmHg) blood pressure, measured at the end of each period of treatment.

**HbA<sub>1c</sub> and daily BG measurements**

HbA<sub>1c</sub> levels achieved at the end of each period of treatment were 7.89 ± 0.77% with CSII and 8.24 ± 0.77% with MDI. HbA<sub>1c</sub> was significantly lower with CSII (P < 0.001). Mean daily BG measurements, recorded during the last 14 days of each period of treatment, were significantly lower with CSII when compared with MDI (CSII 165 ± 27 mg/dl vs. MDI 175 ± 33 mg/dl, P < 0.05).

BG stability was better with CSII than with MDI, as assessed by the difference in the mean SD of BG values during the last 14 days of each study period (CSII 73 ± 15 mg/dl vs. MDI 82 ± 18 mg/dl, P < 0.01) (Table 2).

**Insulin doses**

At baseline, mean insulin doses were 43.6 ± 13.5 U/day. The basal insulin regimen had to be optimized (NPH injection moved from breakfast to noon or added at noon) in 75% of the patients during the MDI period (the mean number of NPH injections was 2.65 per day at the end of the MDI period). The total insulin doses required to maintain glucose control during the MDI treatment period were much higher than those during the CSII period (CSII 38.5 ± 9.8 U/day vs. MDI 47.3 ± 14.9 U/day, P < 0.0001). This difference was mainly due to higher basal insulin requirements in the MDI regimen (CSII 20.8 ± 5.8 U/d vs. MDI 27.5 ± 8.8 U/day, P < 0.03). However, the daily bolus insulin dose was also significantly higher with MDI (CSII 17.7 ± 6.6 U/day vs. MDI 19.8 ± 8.4 U/day, P < 0.04).

**Hypoglycemic events**

During the last 14 days of each treatment period, hypoglycemic events (BG levels <60 mg/dl) occurred at a rate of 3.9 ± 4.2/14 days with CSII and 4.3 ± 3.9/14 days with MDI (NS). Severe hypoglycemic episodes were reported 4 times during the study, 3 times with CSII and 1 time with MDI in 2 patients and 1 patient, respec-

**Table 2—HbA<sub>1c</sub>, capillary BG measurements, and daily insulin doses**

	CSII regimen	MDI regimen	P
HbA <sub>1c</sub> (%)	7.89 ± 0.77	8.24 ± 0.77	<0.001
Mean glycemia (mg/dl)	165 ± 27	175 ± 33	<0.05
Mean SD of BG values (mg/dl)	73 ± 15	82 ± 18	<0.01
Patients with BG level <60 mg/dl	3.9 ± 4.2	4.3 ± 3.9	NS
Total insulin dose (U/day)	38.5 ± 9.8	47.3 ± 14.9	<0.0001
Basal insulin dose (U/day)	20.8 ± 5.8	27.5 ± 8.8	<0.03
Bolus insulin dose (U/day)	17.7 ± 6.6	19.8 ± 8.4	<0.04

Data are means ± SD. HbA<sub>1c</sub> was measured at the end of each period of treatment. Capillary daily BG measurements, SD of BG values, the number of hypoglycemic events, and the insulin doses were measured during the last 14 days of each treatment period.

tively. None of these episodes resulted in coma or seizures. External help was necessary to take glucose, but glucagon or glucose injection was never required.

**Satisfaction**

At the end of the study, the patients were asked which regimen they preferred for the continuation of their therapy. A total of 29 patients chose CSII (21 were previously on CSII with regular insulin, and 8 were previously on MDI), and 11 chose MDI (10 were previously on CSII and 1 was previously on MDI).

**CONCLUSIONS** — CSII has been developed to improve glycemic control of type 1 diabetic patients by means of more physiological insulinization than that with MDI. In the 1980s, several studies comparing the 2 modes of insulin delivery showed a reduction of HbA<sub>1c</sub> ranging from 0.4 to 1% (2–4). However, very few of these studies were randomized (10), baseline HbA<sub>1c</sub> in these patients was high (9–11%), and the injection regimens used were not always as intensified as they are now. In the DCCT, CSII-treated patients maintained a mean HbA<sub>1c</sub> level of 6.8 vs. 7.0% in patients treated by a highly intensified MDI regimen, and this slight difference was significant (11). In our study, the comparison of CSII and an intensified MDI regimen with 5–6 injections per day shows a significant difference of 0.35% in HbA<sub>1c</sub> in favor of CSII. This reduction is slight, but the baseline levels of HbA<sub>1c</sub> were much lower than those in previous studies and therefore one could not expect a very large decrease in HbA<sub>1c</sub>. Moreover, these results were obtained under routine conditions of follow-up (patients being seen every 2 months by their usual physician) and not with an intensified follow-up such as that used in

the DCCT, which might have led to a larger decrease in HbA<sub>1c</sub>.

Three multicenter randomized studies have demonstrated the superiority of insulin lispro over regular insulin in external pumps, the difference obtained in terms of HbA<sub>1c</sub> ranging from 0.1 to 0.6% (7–9). The present work confirms that the replacement of regular insulin by insulin lispro in the pump allows a reduction of 0.5% in HbA<sub>1c</sub> (8.39% at baseline vs. 7.89% on lispro). This difference is probably because of the more physiological kinetics of insulin lispro, which provides a rapid and short prandial insulin peak.

The first studies comparing MDI regimens with regular insulin and insulin lispro showed no difference in HbA<sub>1c</sub>, indicating the need for optimization of basal insulin replacement (12). When the number of NPH injections was optimized, HbA<sub>1c</sub> decreased by 0.3–0.8% in several studies (13–15). Therefore, both CSII studies and MDI studies with optimized basal insulin replacement have shown the superiority of insulin lispro over regular insulin. However, it remained to be elucidated whether the use of insulin lispro was equally efficient on HbA<sub>1c</sub> in an intensified MDI regimen and in CSII. In our study, CSII remains superior to MDI—CSII with lispro combining the beneficial effects of the pharmacokinetics of lispro for the boluses on the one hand, and the better efficacy of basal insulin replacement with a continuous basal rate compared with long-acting insulin on the other hand.

Besides HbA<sub>1c</sub>, the frequency of hypoglycemic events is a major concern in type 1 diabetic patients on intensified treatment. In the intensive therapy group of the DCCT, severe hypoglycemia was slightly more frequent with CSII than with MDI (0.54 vs. 0.44 patient-years) (16). By contrast, several

long-term studies show that CSII with regular insulin can reduce the frequency of severe hypoglycemia (5,6,17). Meta-analysis of studies with insulin lispro also show a reduction in the rate of severe hypoglycemia (18). We found in the present study no significant difference in the frequency of severe and mild hypoglycemia. However, with HbA<sub>1c</sub> improving during CSII, this is a positive result for this treatment.

The SD of glycemia reflects the fluctuations of BG levels. With CSII, the SD of glycemia was significantly lower, indicating improved glycemic stability over the day. This might be related to more reliable absorption of insulin with CSII, using a single injection site for several days, as previously described with regular insulin (19,20), and to better reproducibility of the pharmacokinetic profile of lispro (21).

There is a clear need for the optimization of basal insulin replacement when lispro is used as prandial insulin. This optimization is easy with CSII. During the MDI period, a third injection of NPH had to be rapidly added in most of the patients. The insulin doses required to achieve glycemic control with MDI increased significantly by 22.8%. Using regular insulin, Bode et al. (6) previously reported a reduction of 15% in insulin doses in patients switching from MDI to CSII. In our study, during the MDI period, the increase in NPH doses was marked (32.2%) and was mainly caused by a rise in the bedtime NPH dose, explained by the major difficulties these patients had in achieving near-normal fasting BG levels.

Despite the important rise in insulin doses, no change in body weight or blood pressure was observed in our study. However, it would be worthwhile to evaluate these parameters after a long period of time. On the other hand, the lower insulin requirements with CSII may counterbalance the hypothetical increased tendency for hypoglycemia induced by lower HbA<sub>1c</sub> levels.

At the end of the study, the majority of patients chose CSII with lispro. However, 10 patients previously on CSII with regular insulin chose MDI with lispro. Our study was not designed to compare CSII with regular insulin and MDI with lispro, but this finding indicates that for patients accustomed to CSII with regular insulin, an optimized MDI regimen with insulin lispro, which they had never used before, was able to provide a valuable alternative.

In terms of glycemic control, we conclude that CSII with insulin lispro is superior

to an intensified MDI regimen with insulin lispro; CSII treatment requires lower doses of insulin and does not increase the risk of hypoglycemia. External pump treatment with the short-acting insulin analog lispro seems to us the best way to achieve good diabetes control in type 1 diabetic patients accustomed to intensified insulin therapy.

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