COMPARISON OF BLOOD GLUCOSE STABILITY AND HbA1c BETWEEN IMPLANTABLE INSULIN PUMPS USING U400 HOE 21PH INSULIN AND EXTERNAL PUMPS USING LISPRO IN TYPE 1 DIABETIC PATIENTS: A PILOT STUDY

B. CATARGI (1), L. MEYER (2), V. MELKI (3), E. RENARD (4), N. JEANDIDIER (2) for the EVADIAC Study Group.

SUMMARY - Background: To assess the efficacy on blood glucose control of continuous peritoneal insulin infusion from implantable pump (CPII) compared with continuous subcutaneous infusion using insulin lispro (CSII-IL) in type 1 diabetic patients.

Methods: Fourteen type 1 diabetic patients (5 males and 9 women, age 50.6 ± 12.8, diabetes duration 28.0 ± 13.4 years) were treated with CSII-IL and CPII. Capillary blood glucose (BG) was monitored and recorded at least 4 times per day during 2 study periods of 45 days: using CSII-IL (period A), and from 45th to 90th day after implantation (period B). HbA1c was measured at the end of each period.

Results: Both daily BG levels (145 ± 18 vs 153 ± 17 mg/dl, p < 0.01) and preprandial BG levels (139 ± 20 vs 147 ± 22 mg/dl, p < 0.05) were lower in period B. Although postprandial BG values tended to be lower in period B, this reduction did not reach statistical significance (149 ± 20 vs 157 ± 16 mg/dl, p = 0.07). Meanwhile, SD of all BG values was lower with CPII (11 ± 1 vs 17 ± 17 mg/dl, p < 0.01) and HbA1c levels were lower at the end of period B (7.3 ± 0.9 vs 7.8 ± 0.9%, p = 0.04). Low blood glucose index was comparable during both periods (2.8 ± 1.6 vs 3.1 ± 1.5, p = 0.4).

Conclusion: CPII may provide a better BG control and stability than CSII-IL. However, a long-term randomized prospective study is needed to confirm these improvements.

Key-words: implantable insulin pump, type 1 diabetes, CSII, insulin analog.

RéSUMÉ - Comparaison de la stabilité glycémique et de l’HbA1c entre traitement par pompe implantable avec insuline U400 HOE 21PH et traitement par pompe portable avec analogue rapide de l’insuline chez des patients diabétiques de type 1: une étude pilote.

Contexte : Nous avons comparé l’efficacité de l’insulinothérapie par voie intrapéritonéale (CPII) à celle obtenue par voie sous cutanée à l’aide d’une pompe portable avec analogue rapide de l’insuline (CSII-IL).

Méthodes : Quatorze patients diabétiques de type 1 (5 hommes, 9 femmes, âge : 50.6 ± 12.8 ans, durée du diabète : 28.0 ± 13.4 ans) ont été traités par pompe portable avec Humalog® et par pompe à insuline implantable.

Deux périodes de 45 jours ont été étudiées pendant lesquelles les patients ont réalisé au moins 4 glycémies capillaires par jour : période avec pompe portable (période A) et période après implantation (période B). L’HbA1c a été mesurée à la fin de chaque période.

Résultats : Les glycémies capillaires moyennes (145 ± 18 vs 153 ± 17 mg/dl, p < 0.01) et les glycémies capillaires préprandiales (139 ± 20 vs 147 ± 22 mg/dl, p < 0.05) de la période B sont plus faibles alors que les glycémies capillaires postprandiales ne montrent qu’une tendance (149 ± 20 vs 157 ± 16 mg/dl, p = 0.07). La déviation standard des glycémies capillaires des 24 heures est plus basse en période B (69 ± 11 vs 79 ± 17 mg/dl, p < 0.01) et l’HbA1c meilleure (7.3 ± 0.9 vs 7.8 ± 0.9 %, p = 0.04). Il n’y a pas de différence significative entre les valeurs de LBGI des 2 périodes étudiées (2.8 ± 1.6 vs 3.1 ± 1.5, p = 0.4).

Conclusion : Ces résultats sont en faveur d’un meilleur contrôle et d’une meilleure stabilité glycémique par CPII que par CSII-IL, ils nécessitent cependant d’être confirmés dans une étude prospective randomisée.

Mots-clés : pompe à insuline implantable, diabète de type 1, pompe à insuline portable, analogue de l’insuline.

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he reduced incidence of microangiopathy in the intensively managed group of patients of the DCCT strongly supports the need for a long-term near-normal blood glucose control in type 1 diabetic patients [1]. However, the simultaneous increased frequency of severe hypoglycemic events has clearly documented the need for improved modes of insulin administration. Continuous subcutaneous insulin infusion (CSI) using an external pump is an alternative to multiple daily-injections (MDI). Several reports have shown that CSI helps to achieve lower HbA1c levels and reduce the frequency of severe hypoglycemia compared with MDI [2]. The development of short-acting insulin analogs characterized by a faster onset of action and a shorter half-life was meant to improve subcutaneous insulin kinetic [3, 4]. Insulin lispro in the setting of CSI (CSI-IL) has been shown to decrease HbA1c levels without increasing the risk of hypoglycemia in comparison with CSI using regular insulin [5, 6].

Plasma insulin profiles observed during intraperitoneal insulin infusion (CPII) through portal diffusion have shown a rapid increase, with a sharp insulin peak early after meals and low insulin levels immediately before the next meal [7]. In type 2 diabetes, the use of implantable insulin pump has shown to significantly reduce glyceric variability compared to multiple daily injections [8].

Until now, the comparison of the efficacy between CPII and CSI-IL has only been published in one case report [9], addressing the need to compare the efficacy of these 2 modes of therapy in terms of glycemic control, glyceric stability and hypoglycemia frequency.

## RESEARCH DESIGN AND METHODS

### Patients and study design

Our retrospective, open labeled study was conducted in 4 French centers of the EVADIAC Study Group. Fourteen type 1 diabetic, C-peptide negative patients were studied while treated with CSI (506 or 507 external pumps, MiniMed Technologies, Sylmar, CA, USA) using the rapid insulin analog lispro (Humalog®, U-100, Lilly-France, Saint-Cloud, France) and with CPII (MIP2001 or MIP2007 implantable pumps, MiniMed Technologies, Sylmar, CA, USA). Selection criteria were to be enrolled in the implantable pumps study and to be treated in turn with CSI-IL and CPII. Three patients were first treated with CPII and then with CSI-IL due to technical problems with the implanted devices (battery failure), 11 were treated with CSI-IL prior to implantation as a training to continuous insulin infusion as it is a common procedure in some EVADIAC centers. They all had given their written consent to participate in a long-term study approved by an Ethical Committee that was designed to assess the efficacy of CPII infusion of U-400 HOE 21PH insulin (Aventis®, Frankfurt, Germany). This study protocol and results have been previously published [10].

None of them had any severe or evolutive microvascular complication. They had neither hypoglycemia unawareness nor severe associated disease that could interfere with the observational study since these complications are considered as exclusion criteria for the Hoe21PH in implantable pumps protocol. Patients main characteristics are shown in Table I. Patients had to be seen every 45 days for insulin pump refills. Two periods of 45 days were studied: one while using CSI-IL (period A), the second one extending from 45th to 90th day after implantation (period B). Pumps were implanted and used as previously reported [10]. The volume of insulin solution drained from the pump before the refill was compared with the expected volume computed by the pump communicator to rule out any under delivery or device malfunction.

The first 45 days-period following implantation was not included in the study to avoid BG fluctuations related to post-surgical recovery and to check the pump delivery accuracy during the first insulin.

### Methods

During each 45 days-period, capillary blood glucose (BG) measurements, using One Touch Profile® meters and strips (Lifescan, Roissy, France), were to be performed by patients at least 4 times per day and when symptoms suggesting hypoglycemia occurred. Glycemic goals were 70-120 mg/dl before meals and 120-180 mg/dl, 2 hours after meals and at bedtime. The memory meters were downloaded on a PC computer using In Touch® software (Lifescan, Roissy, France) at the end of periods A and B. Patients were asked to adapt their insulin doses using the glycemia recorded in their log book during the last 3 to 5 days.

Glycemic fluctuations were assessed, by calculating the mean of the daily standard deviations during the 2 periods.

The risk for severe hypoglycemia during the next 6 months was further assessed by calculating the low
blood glucose index (LBGI) which combines in a single number not only the percentage of low BG readings but also their magnitude in the lower BG range as previously described. This LBGI has been validated as defining the risk for a patient to present a severe hypoglycemic episode during human insulin therapy administered by multiple subcutaneous injections [11]. Briefly, a logarithmic-type BG data transformation, that symmetrizes the BG measurement scale, is performed using the formula: Transformed BG = 1.509 × ((log (BG)) 1.084-5.3811 (BG being expressed in mg/dl). BG readings > 114 mg/dl (6.25 mmol/l) received zero weights and readings < 114 mg/dl were assigned progressively increasing weights, with the highest being at 100 at a BG = 20 mg/dl (1.1 mmol/l). The LBGI was computed as the average weight of all BG readings collected by the patient over one month. LBGI < 5 indicates a low or moderate risk and LBGI > 5 a high-risk [12] for severe hypoglycemia for the next 6 months.

HbA\textsubscript{1c} was measured by high-performance liquid chromatography (normal range 3.0-6.0%) at the end of each study period.

### Statistical analysis

Calculations were performed using the Statview* 4.5 Statistical Software Program (Abacus Concepts, Berkeley, CA). All results are given as mean ± SD. Statistical tests were based on a two-tailed test at a type I error of 5%. Paired t-test was used after logarithmic-type symmetrization of BG data (see above) to compare mean BG levels and LBGI at the end of each treatment period. Statistical significance was inferred at a value of P < 0.05.

### RESULTS

The results of this study are summarized in Table II.

- Daily BG measurements: A total of 5,805 BG measurements (2,854 in period A, 2,951 in period B) was recorded and analyzed. This represents a mean of 4.5 glycemia per day in period A and 4.7 glycemia per day in period B. Cumulated BG measurements for the 14 patients were not different between the two study periods (203.8 ± 46.2 and 210.7 ± 44.8 mg/dl, respectively).

<table>
<thead>
<tr>
<th>BG (mg/ml)</th>
<th>CSII with LP</th>
<th>IP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BG</td>
<td>153.3 ± 17.3</td>
<td>145.4 ± 18.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Preprandial BG</td>
<td>147.5 ± 21.8</td>
<td>139.9 ± 20.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Postprandial BG</td>
<td>157.5 ± 15.7</td>
<td>148.8 ± 20.3</td>
<td>0.07</td>
</tr>
<tr>
<td>SD of BG values</td>
<td>78.8 ± 17.3</td>
<td>69.2 ± 2.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% BG in target</td>
<td>50.6 ± 8.6</td>
<td>57.3 ± 6.8</td>
<td>0.08</td>
</tr>
<tr>
<td>% BG &gt; target</td>
<td>33.7 ± 9.8</td>
<td>28.0 ± 8.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% BG &lt; target</td>
<td>15.6 ± 8.6</td>
<td>14.5 ± 6.9</td>
<td>0.6</td>
</tr>
<tr>
<td>LBGI</td>
<td>2.8 ± 1.6</td>
<td>3.1 ± 1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>HbA\textsubscript{1c} (%)</td>
<td>7.8 ± 0.9</td>
<td>7.3 ± 0.8</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Data are means ± SD. BG, blood glucose. LBGI, low blood glucose index.

HbA\textsubscript{1c} value was significantly lower at the end of period B. Low blood glucose index was comparable during periods A and B.

### DISCUSSION

In recent studies, CSI-IL has been shown to lower HbA\textsubscript{1c} levels when compared during a cross-over randomized study with CSII using regular insulin [5] and to reduce BG fluctuations when compared with an intensified MDI regimen using insulin lispro [13]. It may be considered as the “gold standard” of the insulin therapy used nowadays in clinical practice.

Our study is definitely a retrospective, open labeled, short observational study comparing 2 periods of different treatments in a non-randomized order, but our results show a significantly beter blood glucose control and stability with CPII compared to CSII and Humalog*.

One might consider that our patients could have been more compliant during the CPII period than during the CSII period, this is difficult to completely rule out but HbA\textsubscript{1c} levels obtained with CSII-IL in our study are comparable with those published in a previous report (i.e. 7.6-7.9%) [7]. This demonstrated that our patients diabetes management was comparable to the published CSII-IL studies. Besides, this eventual bias of patients being more compliant during CPII would not be avoided by a randomized study. Intraperitoneal insulin infusion using implanted devices has
been developed from the conceptual advantage of insulin delivery through portal circulation, allowing more physiological insulin distribution and lower peripheral insulinema [14, 15]. Long-term data on BG control during feasibility studies of IP conducted by the EVADAC Study Group have shown lower HbA1c levels, reduced BG fluctuations and a dramatically decreased occurrence of severe hypoglycemic events. These results were sustained for 30 months, when compared with MDI or CSII regimens using regular insulin [16, 10]. These improvements were lost after interruption of IP use [17] showing an improvement directly linked to the IP route of administration of insulin. This is why it became very interesting to compare the peritoneal mode of administration with the new “gold standard” of clinical insulin therapy.

Our metabolic data during period B of the present study are similar to those obtained during the corresponding early phase of EVADAC studies. This confirms in part the validity of the short term results of this study. Since underdelivery incidents reported with IP during the 1993-97 period [18] have been solved by the availability of more stable insulin preparations [19] and the design of a new sideport catheter [20], we may expect that our present results should be sustained on a long term basis.

From our preliminary results, the main benefit on BG control during IP use compared with previous CSII-IL relies on significantly reduced preprandial BG levels and glycemic fluctuations assessed by SD during CPII. Interestingly, preprandial BG values were not improved in studies comparing CSII with regular insulin vs insulin lispro [5]. Since preprandial BG levels were lowered during CPII, we may suggest that basal insulin delivery using the peritoneal route could be more efficient than CSII-IL in suppressing hepatic glucose production in fasting and late post-absorptive conditions. This could be due to the direct and more physiologic portal absorption inducing a first hepatic insulin passage through the liver [14].

The choice of the 24H glycemic standard deviation as a parameter of glycemic fluctuations and thus glycemic stability has been conducted by the fact that this parameter is considered as a simple index commonly used by numerous authors [6, 10, 21-23] allowing to compare results between studies. The criteria defining stable or unstable diabetes are commonly accepted and validated [21]. The SD limitations are due to the fact that it is a dispersion parameter and that its sensitivity is considered as low. Thus a significant variation in a short period of time comforts the importance of the discrepancy between the 2 modes of therapy. A restoration of glucagon response to hypoglycemia has been described with CPII [24] and this may contribute to the improvement of glycemic fluctuations during CPII. This observation, if confirmed in prospecstive randomized studies would show the interest of CPII in brittle diabetes and would define the clinical indication of this mode of therapy. Our SD results remain quite high in our study [20]. Patients chosen to be treated with CSII -IL have usually unstable diabetes and this may explain these high results, while in the published studies patients are randomized and would not necessarily need such a treatment.

Computed LBGI to assess the risk for severe hypoglycemia remained in the moderate range [24] with the two modes of insulin therapy. Since 130 self-monitored BG readings spread over 4-5 weeks are sufficient to accurately calculate the LBGI, our computed data could be considered as valid [12]. However, it must be kept in mind that this index has been shown to be a reliable predictor of severe hypoglycemia only in type 1 diabetic patients treated with MDI using regular insulin [25]. Until further specific validation for treatments with insulin lispro, CSII and peritoneal insulin delivery, LBGI might be unable to provide any accurate estimation of risk for severe hypoglycemia, or have a poorly discriminating power while using or comparing these treatment modes. Thus, any drawn conclusion from LBGI in this study is probably premature.

**CONCLUSION**

Although limited to a short-term, retrospective, pilot observational study, our results suggest that CPII may provide some additional metabolic benefits to CSII-IL, in terms of glucose control and glycemic fluctuations for patients whose indication of continuous insulin infusion had been chosen for unstability and difficulty in the management of diabetes. The specific hepatic first passage due to the peritoneal route and portal absorption might explain the better BG control in the late post-absorptive periods and the subsequently improved BG stability. Further data obtained from a prospective randomized long-term study are undoubtedly necessary to confirm the preliminary results presented here.

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