A RANDOMIZED STUDY COMPARING BLOOD GLUCOSE CONTROL AND RISK OF SEVERE HYPOGLYCEMIA ACHIEVED BY NON-PROGRAMMABLE VERSUS PROGRAMMABLE EXTERNAL INSULIN PUMPS

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SUMMARY - Objective: To compare a non-programmable and a programmable insulin external pump using regular insulin on glycemic stability, the risk of severe hypoglycemia and metabolic control in type 1 diabetic patients.

Material and methods: Ten type 1 diabetic patients were involved in a randomized, crossover study comparing two periods of 3 months with continuous subcutaneous insulin infusion (CSII) either with a non-programmable insulin pump or a programmable insulin pump. Comparisons were made among mean blood glucose values before and after meals, at bedtime and at 2:00 a.m.; the risk of severe hypoglycemia assessed by the low blood glucose index (LBGI); and HbA1c.

Results: Mean average blood glucose (BG) measurements were significantly lower with the programmable in comparison with the non-programmable insulin pump (respectively 157±78 vs. 165±79, p=0.034). While postprandial values for BG were not different between the two pumps, the use of the programmable pump resulted in a significant decrease in mean preprandial BG levels (140±68 vs. 150±73 mg/dl p=0.039). Conversely mean BG level was lower at 2 a.m. with the non-programmable pump (125±81 vs. 134±83 mg/dl, p=0.02) but with a higher incidence of hypoglycemia. Mean LBGI was comparable with the two pumps (3.1±8.6 vs. 2.8±6.9, p=0.1). There was a 0.2% decrease in HbA1c during the programmable pump period that did not reach statistical significance (p=0.37).

Conclusions: The present study suggests that programmable external insulin pumps, although more complex and more expensive than non-programmable insulin pumps, significantly reduce fasting glycemia during the day without increasing the risk of severe hypoglycemia and are safer during the night.

Key-words: insulin pump, programmability, glycemic control, low blood glucose index, hypoglycemia, randomized study.

RÉSUMÉ - Etude comparative du contrôle glycémique et du risque d’hypoglycémie obtenus par pompe à insuline non programmable et programmable.

Objectifs : Comparer l’équilibre glycémique, le risque d’hypoglycémie sévère et l’HbA1c obtenus par pompe à insuline externe programmable et non programmable.

Matériel et méthodes : Dix patients diabétiques de type 1 ont été tirés au sort pour porter soit une pompe non programmable, soit une pompe programmable pendant 3 mois avant de changer de type de pompe pendant les 3 mois suivants. Nous avons comparé les glycémies pré- et postprandiales, à 2 heures du matin ainsi que l’HbA1c à la fin de chaque période. Le risque d’hypoglycémie a été évalué par le LBGI (Low blood Glucose Index).

Résultats : La pompe programmable a permis d’obtenir une glycémie moyenne plus basse par rapport à la pompe non programmable (157±78 vs. 165±79 mg/dl, p=0.034). La glycémie moyenne à jeun durant la journée était plus basse avec la pompe programmable par rapport à la pompe non programmable (140±68 vs. 150±73 mg/dl p=0.039) alors que la glycémie postprandiale n’était pas significativement différente. Inversement la glycémie à 2 heures du matin était plus basse avec la pompe non programmable (125±81 vs. 134±83 mg/dl, p=0.02) mais moyennant une incidence d’hypoglycémies plus élevée. Le LBGI était comparable entre les deux types de pompes (3.1±8.6 vs. 2.8±6.9, p=0.1). Enfin nous avons observé une diminution non significative de 0,2 % de l’HbA1c avec la pompe programmable.

Conclusions : Notre étude suggère que les pompes à insuline externes programmables bien que plus coûteuses et de maniement plus difficile permettent d’obtenir des glycémies à jeun plus basses sans augmenter le risque d’hypoglycémie sévère et sont plus sûres durant la nuit.

Mots-clés : pompes à insuline externe, contrôle glycémique, risque d’hypoglycémie, étude randomisée.
he demonstration in the 9 year DCCT trial that optimal glycemic control dramatically delayed the onset and reduced the risk of the progression of microvascular complications illustrated the need to improve modes of insulin replacement [1]. Within the group of intensively treated subjects, continuous subcutaneous insulin infusion (CSII) achieved lower HbA1c levels than multiple daily injections (MDI). The limited local insulin depot during continuous subcutaneous insulin infusion (CSII) therapy is thought to induce a more constant and reproducible regular-insulin absorption [2] resulting in fewer day-to-day fluctuations in blood glucose concentrations [3] and in fewer episodes of hypoglycemia [4]. Furthermore, the opportunity of a step-up in the overnight basal insulin delivery with CSII reduces dawn hepatic glucose production and contributes to the improvement of glycemic control [5]. On the other hand the local insulin depot delays for several hours the change in the insulin absorption rate following a change in the basal insulin rate [6], and a marked dawn phenomenon in type 1 diabetic patients is not only infrequent, but when present its reproducibility is still poorly understood.

Programmable pumps are potentially superior and safer to non-programmable pumps but the additional cost (8 000 FF for a non-programmable pump and 21 000 FF for a programmable one) makes the assessment of these possible benefits necessary. Therefore we designed a prospective study to question the advantage, if any, of basal programmability of external insulin pumps in both blood glucose fluctuations and assessment of risk of severe hypoglycemia under routine conditions in Type 1 diabetic patients.

**Study design**

The study protocol was approved by the local Ethical Committee and all patients gave written consent to the study. The study was designed to be a randomized crossover open study. After a 4-week run-in period of treatment with a programmable pump, patients were randomly assigned to use either a non-programmable or a programmable (allowing 6 different basal rates) external insulin pump (MiniMed 505 or 506, Sylmar, CA, USA, respectively) for 3 months before crossing over to the other pump for another 3 months.

**Patients**

Ten patients, 4 females and 6 males aged 37.2 ± 13.8 y.o. (26 to 66) with a BMI of 24.1 ± 2.1 kg/m² and a diabetes duration of 16.1 ± 7.7 y.o., were included in the study. None of them had significant endogenous insulin secretion (C-peptide < 0.3 ng/ml), untreated retinopathy, hypoglycemia unawareness, impaired renal function or any other severe disease that could interfere with the study. Patients were transferred to CSII treatment according to usual guidelines [7] since they were unable to achieve acceptable control under multiple daily injections and self-monitoring of blood glucose (mean HbA1c 8.5 ± 1.5%). During the initiation and the run-in period on programmable CSII, they all required at least 2 to 5 different basal insulin infusion rates, with a mean low rate of 0.6 ± 0.1 U/h and a mean high rate of 1.2 ± 0.5 U/h.

Of importance, all patients required a step increase in the basal infusion rate during the night based on the rise in blood glucose monitoring. Adjustments of the insulin regimen were made by the patient based on the results of self-monitoring, and by the investigator at a 1-month study visit interval using algorithms previously described [8].

Patients used regular human insulin Velosulin U-100 (Novo Nordisk, Boulougne-Billancourt, France), and the infusion site and catheter were changed every 3 days. Moreover, they were told to follow the same diet and avoid snacks during the study. Patients were asked to perform 5-7 daily capillary blood glucose (BG) measurements and weekly at 2 a.m. using One Touch Profile meters and strips (Lifescan, Roissy, France). Treatment goals were 80-160 mg/dl during fasting periods and 120-180 mg/dl 2 h after meals and at bedtime. The memory meters were downloaded on a PC computer using In Touch software (Lifescan, Roissy, France). The risk of severe hypoglycemia was 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 [9].

Briefly, after a logarithmic-type BG data transformation using the formula: Transformed BG = 1.509 × [(log (BG)]^{1.084} - 5.381] the BG readings > 112.5 mg/dl (6.25 mmol/l) received zero weights and readings ≤ 112.5 mg/dl are assigned progressively increasing weights, with the highest being at 100 at a BG = 20 mg/dl (1.1 mmol/l) [10]. Finally the LBGI is computed as the average weight of all BG readings.

LBGI < 5 indicates a low or moderate risk for future severe hypoglycemia and LBGI > 5 a high-risk. HbA1c was measured by high-performance liquid chromatography (Menarini Diagnostics, Florence, Italy; normal range 3-6%) at the end of each study period.

**Statistical analysis**

Calculations were performed with the Statview 4.5 Statistical Software Program (Abacus Concepts, Calabasas, CA, USA). Results are given as means ± SD or otherwise stated. Statistical tests were based on a two-tailed test at a type 1 error of 5%. ANOVA for
repeated measures was used after logarithmic-type symetrisation of BG data (see above) to compare mean BG levels during each treatment period. Statistical significance was inferred at a value of $P < 0.05$.

**RESULTS**

**BG measurements and control**

A total of 6,526 BG measurements were recorded during the study including 3,246 measurements with the non-programmable insulin pump (1990 preprandial) and 3,280 with the programmable insulin pump (1880 preprandial).

As training may have had a significant effect on BG stability, particularly with the programmable pump, we ensured that SD was stable during the two periods and that BG-by-time interaction was not significant (data not shown) (Fig. 1).

We found that mean daily and mean preprandial BG levels achieved with the programmable pump were lower in comparison with the non-programmable pump, while postprandial BG levels were not different. Conversely mean BG level was lower at 2 a.m. with the non-programmable pump (125 ± 81 vs. 134 ± 93, $p = 0.02$).

**FIG. 1.** Self-monitored daily capillary blood glucose (BG) in ten type 1 diabetic patients using a non-programmable insulin pump (open circles) and a pre-programmable insulin pump (closed circles) for 3 months. * $p < 0.05$. Values represent means ± SEM.

**TABLE I.** Capillary BG measurements, HbA1c and daily insulin doses during each treatment period. Footnote data are means ± SD. LBGI, low blood glucose index. BG, blood glucose.

<table>
<thead>
<tr>
<th></th>
<th>Non-programmable pump</th>
<th>Programmable pump</th>
<th>$P$</th>
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<tbody>
<tr>
<td>BG (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glycemia</td>
<td>165 ± 79</td>
<td>157 ± 78</td>
<td>0.034</td>
</tr>
<tr>
<td>Preprandial glycemia</td>
<td>150 ± 73</td>
<td>140 ± 68</td>
<td>0.039</td>
</tr>
<tr>
<td>Postprandial glycemia</td>
<td>188 ± 82</td>
<td>179 ± 83</td>
<td>0.11</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 1.3</td>
<td>7.2 ± 1.0</td>
<td>0.37</td>
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<tr>
<td>LBGI</td>
<td>2.9 ± 6.9</td>
<td>3.1 ± 8.5</td>
<td>0.18</td>
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<tr>
<td>Daily insulin doses (IU/kg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Basal rate</td>
<td>0.32 ± 0.02</td>
<td>0.29 ± 0.02</td>
<td>0.34</td>
</tr>
<tr>
<td>Bolus</td>
<td>0.30 ± 0.02</td>
<td>0.30 ± 0.02</td>
<td>0.93</td>
</tr>
<tr>
<td>Total</td>
<td>0.62 ± 0.01</td>
<td>0.59 ± 0.03</td>
<td>0.39</td>
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</table>
Hypoglycemic events

The LBGI index was less than 5 during the 2 periods and was not statistically different.

The number of total hypoglycemia (defined as blood glucose values < 54 mg/dl) at 2 a.m. was 23 with the non-programmable pump and 11 with the programmable pump. There were no severe hypoglycemic events during the study in either period as defined by the Diabetes Control and Complications Trial (DCCT) criteria [1].

HbA1c

There was no significant change in the mean HbA1c values (Table I).

Other results

We did not observe any significant difference in BMI (respectively 24.2 ± 1.9 vs. 24.1 ± 2.0 kg/m²) nor in total daily insulin dose (0.62 ± 0.01 vs. 0.59 ± 0.03 U/kg) between the two periods.

During the study, there were no apparent catheter occlusions.

## DISCUSSION

The investigation of CSII kinetics has led to the development of programmable insulin pumps, even if physiological insulin replacement continues to be an elusive goal [11]. Programmed changes in basal insulin delivery aims to prevent a high hypoglycemia risk (especially occurring nocturnally) or to compensate for the increased insulin need that accompanies the dawn phenomenon.

However, doubling the infusion rate does not affect the absorption rate at least for the following 3 hours and a previous report demonstrated that the early morning rise in blood glucose may be best treated by an increased whole-day basal infusion rate [12], which raises the question of the relevance of nocturnal infusion-rate change(s) [6], at least when using regular insulin.

We compared two types of insulin-delivering pumps in a crossover randomized prospective study and we found that mean daily and logically preprandial BG levels achieved with the programmable pump were lower in comparison with the non-programmable pump, while postprandial BG were not different. As we chose in the present study “safe” target blood glucose and consequently safe basal rates we did not observed any severe hypoglycemic events in either period. Interestingly, the decrease in mean BG with the programmable pump was not only related to any increase in the risk for severe hypoglycemic events as assessed by LBGI but the programmable pump seemed also safer at 2 a.m. than the non-programmable pump. As at least 130 self-monitoring readings spread over 4-5 weeks are sufficient to accurately calculate the LBGI our data can be considered valid [9].

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. Until further specific validation for treatments with CSII, 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. Conversely our strategy could have explain only a 0.2% reduction in HbA1c levels between the two periods. Thus reducing the morning rise of BG by increasing the basal infusion rate may not be sufficient to improve metabolic control as assessed by HbA1c. However we cannot exclude that the limited number of patients, the limited duration of the study, or the decrease of glycemia at 2 a.m. with the non-programmable pump contributed to the failure to demonstrate a significant reduction in HbA1c. Nevertheless, we not only analyzed a weekly glucose profile, but all BG measurements stored in the glucose meters for 6 months, representing more than 6500 measurements. Therefore, at least the interpretation of diabetes profile and the frequency of hypoglycemic events are probably meaningful here.

Obtaining normoglycemia as safely as possible (i.e. without increasing the risk of hypoglycemia) may be achieved in two different ways with a non-programmable insulin pump. The first is to maintain a constant basal rate of insulin infusion and to add snacks in order to prevent hypoglycemia in case of borderline BG levels or before physical exercise. We adopted the second approach in which the diet intake was kept constant while the basal infusion rate was modified according to BG levels particularly at bedtime. This procedure may have explained a stable BMI and in total daily insulin dose between the two periods.

We conclude that pre-programmable external insulin pumps, although more complex and more expensive than non-programmable insulin pumps, significantly reduce fasting glycemia without increasing the risk of severe hypoglycemia. Advantage of programmability of CSII on metabolic control assessed by HbA1c has now to be confirmed with the use of insulin analogues [13, 14] that harbor shorter kinetics than regular insulin.

Acknowledgments – This work was supported by a Grant of the University Hospital of Bordeaux.
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