Long-term treatment combining continuous subcutaneous insulin infusion with oral hypoglycaemic agents is effective in type 2 diabetes

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Abstract

Aim. – To compare over 3 years the efficacy of two treatment regimens combining continuous subcutaneous insulin infusion (CSII) and oral hypoglycaemic agents (OHA) in type 2 diabetic patients with HbA1c levels > 8% despite OHA ± insulin.

Methods. – Fifty-nine patients were randomized to two groups. In both groups metformin was continued; CSII (velosulin) was used with minimal manipulation. Group A: the optimization of insulin doses was exerted on boluses to achieve postprandial glycaemia < 9.99 mmol/l. Sulfonylurea, administered as a single dose at bedtime, was adjusted to attain fasting glycaemia < 6.66 mmol/l. Group B: the optimization of insulin doses was exerted on night time basal rate to attain fasting glycaemia < 6.66 mmol/l. Sulfonylurea, given before each meal, was adjusted to obtain postprandial glycaemia < 9.99 mmol/l.

Results. – During the 3 years follow-up, overall mean HbA1c values decreased similarly for both groups from baseline (9.45 ± 0.83%) to 1, 2, 3 years (7.76 ± 0.85%; 8.06 ± 1.10%; 8.27 ± 1.06% \( P < 0.0001 \)). The mean frequency of minor hypoglycaemia was 1.3 ± 2.3 events per month per patient and 14 severe hypoglycaemic events occurred with no difference between the two groups. In both groups we observed a significant and similar weight gain and improvement in quality of life.

Conclusion. – Long-term combination therapy with OHA and CSII with only basic manipulation and optimization of insulin doses exerted on basal rate or on boluses is feasible, effective and well accepted in type 2 diabetes.

Résumé

L’association pompe à insuline portable et hypoglycémiant oraux est efficace à long terme dans le diabète de type 2

Objectif. – Comparer à trois ans l’efficacité de deux modalités thérapeutiques associant pompe à insuline externe et hypoglycémiant oraux, chez des diabétiques de type 2 déséquilibrés (HbA1c > 8 %) malgré des hypoglycémiant oraux ± insuline.


Résultats. – Pendant les trois ans de suivi, l’HbA1c, moyenne s’est améliorée de manière similaire dans les deux groupes : 9,45 ± 0,83 % à j0 vs. 7,76 ± 0,85 % ; 8,06 ± 1,10 % ; 8,27 ± 1,06 % (\( P < 0,0001 \)) à un, deux, trois ans. La fréquence moyenne des hypoglycémies mineures a été de 1,3 ± 2,3 épisodes par mois par patient et nous avons observé au total 14 hypoglycémies sévères sans différence selon les groupes. Nous avons observé de manière significative et similaire entre les groupes une prise de poids et une amélioration de la qualité de vie.
1. Introduction

The UK Prospective Diabetes Study (UKPDS) [1] has demonstrated that satisfactory long-term glycaemic control can prevent the microvascular complications of type 2 diabetes. In a large number of patients, the failure of conventional treatments leads to the need for new treatment regimens. Continuous subcutaneous insulin infusion (CSII) via an external pump has proved its efficacy on the reduction of HbA1c levels in type 1 diabetes [2–6]. However, few studies have examined its use in type 2 diabetes. Two recent studies comparing CSII and multiple daily injections (MDI) [7,8] reported similar improvement in HbA1c at 24 weeks and 1 year in these patients. In another [9] CSII appeared to be superior to MDI in reducing HbA1c in more overweight patients presenting higher HbA1c levels. However, the studies were of relatively short duration and it is debatable whether these results are maintained over time. Moreover, in spite of the association of oral hypoglycaemic agents (OHA) and insulin being well known to limit weight gain, none of these studies used sulfonylurea and CSII in combination.

On another hand, physicians may be reluctant to prescribe CSII in poorly controlled type 2 patients, because of concerns about the ability of the patients to learn and maintain adequate CSII management. Difficulties might particularly lie in the need to develop technical skills in the use of the pump. Therefore it should be of interest to propose as simple a CSII regimen as possible to these patients.

We report the results of a prospective randomized study, which aimed at proposing new therapeutic solutions to type 2 diabetic patients with chronic poor glycaemic control in spite of attempts to optimize their treatment and reinforcement of education. The main objective was to compare over 3 years, the efficiency of two different regimens of intensified treatment combining simple use CSII and OHA on glycaemic control and quality of life.

2. Research design and methods

2.1. Patients and procedures

Patients included in the study were seen alternately by their usual diabetologist and the Diabetology Department of Rangueil University Hospital (Toulouse, France), every month during the first 3 months, then every 45 days for the next 3 months, then every 2 months for 3 years. All of these diabetologists were member of the GEDEC Study Group (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 three times a year and work in collaboration with the University Hospital. Each time they came in the hospital, the patients had a follow-up visit with the physician, the dietician and the nurse.

Patient inclusion criteria were type 2 diabetes, age 40–70 years, body mass index (BMI) 25–40 kg/m², waist to hip ratio > 1, positive C-peptide, negative anti-GAD antibodies and HbA1c levels > 8%, in spite of maximal doses of OHA alone or in combination with insulin and adequate compliance with nutritional and lifestyle guidelines.

We excluded patients with type 1 diabetes, contraindication to sulfonylureas or metformin, preproliferative or proliferative retinopathy, unstable angina or arterial disease, myocardial infarction in the previous 6 months, severe chronic or inflammatory disease or long-term corticosteroid treatment.

All patients gave written informed consent. The study was performed in accordance with the Declaration of Helsinki and with the approval of local independent review boards.

2.2. Study design

Three months after applying to an educational program, patients whose HbA1c was still > 8% were hospitalized for temporary intensified intravenous insulin therapy in order to normalize blood glucose levels and to learn how to use of the external insulin pump (Minimed 506, Minimed, Sylmar, CA, USA), the educational program being limited to basic functions and safety features. They were then randomized in two groups: (Fig. 1) the optimization of insulin doses was exerted either on boluses (group A) or on basal rate (group B). In order to limit weight gain, we restricted basal insulin infusion rate during day and night time in group A, and only on day-time in group B:

- in group A, the pump delivered Velosulin U 100 (Novo Nordisk, Bagsvaerd, Denmark) with a fixed basal rate < 0.25 U/kg per day and preprandial boluses adjusted to achieve postprandial glycaemia < 9.99 mmol/l. Sulfonylurea (gliclazide 80–160 mg, glipizide 5–10 mg, or glibenclamide 5–10 mg) was administered as a single dose at bedtime, adjusted to attain fasting glycaemia < 6.66 mmol/l;
- in group B, the pump delivered velosulin U 100 (Novo Nordisk, Bagsvaerd, Denmark) with a fixed day-time basal rate < 0.25 U/kg per day. Nighttime basal rate (22–7 h) was adjusted by increments of 0.2 U/h, in order to attain fasting glycaemia < 6.66 mmol/l.

Conclusion. – L’association hypoglycémiants oraux et pompe à insuline externe utilisée simplement en optimisant, soit le débit basal, soit les bolus est faisable, efficace et bien tolérée à long terme dans le diabète de type 2.

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Keywords: Type 2 diabetes; Continuous subcutaneous insulin infusion; Glycaemic control; Antidiabetic oral agents; Quality of life

Mots clés : Diabète de type 2 ; Pompe à insuline externe ; Équilibre glycémique ; Antidiabétiques oraux ; Qualité de vie
Sulfonylurea (gliclazide 80 mg, glipizide 5 mg, or glibenclamide 5 mg) were given before each meal and adjusted to obtain postprandial glycaemia < 9.99 mmol/l.

Pump manipulation was restricted a minimum to allow access to CSII to a wide patient population. In both groups basal rate, the physician adapted bolus and sulfonylurea posology. Patients only had to fill the pump reservoir, to change the catheter in respect of safety procedures and to program the boluses in group A. If necessary, pump parameter modifications (excepted boluses) were executed by the physician during a visit or by the patient under control of the physician during a telephone call. Metformin was continued in both groups at the maximal tolerated doses.

A capillary blood glucose memory meter (One Touch Profile®, Lifescan Inc., Milpitas, CA, USA) was given to the patient, who was asked to monitor capillary blood glucose at least six times a week (including fasting, pre- and postprandial measurements) plus one nocturnal measurement per month. The data were downloaded using InTouch software (Lifescan), computing mean capillary blood glucose levels over the previous 30 days. Treatment was adjusted according to self-monitoring of blood glucose levels (SMBG), either during a visit or after a telephone call from the patient.

After 6 months, if compliance with pump treatment was poor for physical and/or psychological reasons, a switch to MDI regimen was proposed. In patients who did not respond to the treatment (HbA1c levels below 8% on two consecutive determinations during the first year), free adjustments of treatment were allowed after 1 year: a second nocturnal basal rate could be added in group A, and boluses in group B. The prescription of sulfonylureas could also be modified.

2.3. Safety assessments

Safety assessments included adverse events, physical examination findings, acute hyperglycaemic episodes related to catheter obstruction and hypoglycaemic episodes. Severe hypoglycaemia was defined as events requiring assistance of a third party. Minor hypoglycaemia was defined as symptoms of hypoglycaemia confirmed by blood glucose meter reading < 3.33 mmol/l.

2.4. Assays

Fasting blood glucose (FBG) was measured by enzymatic method using Olympus AU2700 analyzer (Olympus, Tokyo, Japan), HbA1c by cation-exchange reverse-phase chromatography using a Menarini HA 8160 analyzer (Menarini Diagnostics Ltd., Florence; Italy) (normal range: 4–6%) and C-peptide on an ADVIA Centaur calibrator (Bayer Diagnostics Corporation, New York, USA).

Quality of life was assessed by administration of a questionnaire developed by MAPI Values (MAPI Values French Office, Lyon, France), which included items from the French versions of the 36-item short-form health survey (SF36), Diabetes Quality of Life (DQOL) and Diabetes Treatment Satisfaction Questionnaire (DTSQ). Checking of internal reliability, validity of the criteria and sensitivity to change over time of the questionnaires as well as statistical interpretation were performed by MAPI Values.

2.5. Statistical analysis

Statistical analysis was performed using the SAS statistical software, release 8.2 (SAS Institute Inc., Cary, NC, USA). In bivariate analysis, Chi² test or Fischer’s exact test when appropriate was used to compare the distribution of qualitative variables between the groups, and means of quantitative variables were compared by Student’s t-test. An intention-to-treat analysis was done using mixed model analysis for longitudinal variables to test the change (adjusted for baseline values) in mean HbA1c, weight gain and insulin requirements. Results are presented as mean ± S.D. or number (%). A P value < 0.05 was interpreted as statistically significant.

3. Results

3.1. Subjects

A total of 86 patients were enrolled in this study. Twenty-seven patients were not randomized: 14 maintained HbA1c levels < 8% for at least 2 years after the educational program, five had positive anti-GAD antibodies, two had extremely painful neuropathy justifying the initiation of CSII earlier than required by the protocol, one patient withdrew and five
presented various severe diseases. Fifty-nine patients were randomized. Seven patients were excluded after randomization: six for safety reasons (voluntary and repeated protocol transgression by the patient in pump management) and one patient whose HbA1c had become impossible to interpret because of blood transfusions. One patient was lost to follow-up after relocation overseas. The characteristics of the 51 remaining patients are given in Table 1.

Twelve non-responders (six in group A and six in group B) did not attain the first year HbA1c target. Their results are presented within their respective randomization groups. Their baseline characteristics and their differences from responders are given in Table 2.

Lastly, five patients (four in group A vs. one in group B, \( P = \text{ns} \)) switched from CSII to MDI after more than 6 months as allowed by the protocol. Their results are presented within their respective randomization groups.

As statistical analysis was carried out on the intention-to-treat principle the results of the 12 non-responders patients and the five patients who switched from CSII to MDI have been computed within their respective randomization groups.

### 3.2. Efficacy

Whatever the group, combination therapy with CSII and OHA resulted in significantly improved glycaemic control. Change in HbA1c over the 3-year study period for the two groups taken together was \( 9.45 \pm 0.83\% \) at baseline, \( 7.76 \pm 0.85\% \) at 1 year, \( 8.06 \pm 1.10\% \) at 2 years, \( 8.27 \pm 1.06\% \) at 3 years \( (P < 0.0001) \) and was similar in both groups (interaction non-significant) after adjustment for baseline HbA1c (Fig. 2a).

FBG changed differently over time in the two groups (interaction \( P = 0.0005 \)), showing no change in group A \( (8.77 \pm 3.50 \text{ mmol/l at baseline vs. } 10.21 \pm 3.16 \text{ mmol/l at } 3 \text{ years}) \) and decreasing in group B \( (9.44 \pm 2.11 \text{ mmol/l at baseline vs. } 6.88 \pm 2.11 \text{ mmol/l at } 3 \text{ years}) \).

Compliance to SMBG was better than the minimum required and was maintained throughout the 3 years (change in both groups taken together \( P = \text{ns} \)). The frequency of SMBG remained significantly higher in group A (mean \( 3.8 \pm 1.1 \) vs. \( 3.2 \pm 1.1 \) SMBG determinations per day for the duration of the study, group A vs. group B \( P < 0.01 \), interaction not significant). Mean difference between pre and postprandial SMBG measurements was lower in group A than in group B \( (+1.02 \pm 0.12 \text{ vs. } +1.57 \pm 0.14 \text{ mmol/l, } P < 0.004) \).

Daily insulin doses increased significantly over the 3 years (baseline \( -3 \) years for both groups together, \( P < 0.0001 \)), but the mean dose in group A was significantly higher than in group B (group A vs. group B \( P < 0.01 \), interaction not significant). At the end of the study, patients in group A used more insulin than those in group B (group A \( 0.73 \pm 0.12 \text{ U/kg per day vs. group B } 0.50 \pm 0.02 \text{ U/kg per day, } P < 0.005 \) (Fig. 2b).

Daily sulfonylurea doses increased over the 3 years. As allowed by the protocol, mean doses were significantly higher in group B. At the end of the study, 79% of group B patients received 15 mg glibenclamide per day while 70% of group A patients received 5–10 mg glibenclamide per day. In group B two patients (8%) and in group A three patients (11%) presented a contraindication to sulfonylurea during the study.

As described in protocol, metformin doses remained constant along the study. At the end of the study, 84% of the patients received 2550 mg daily, 6% of the patients 1700 mg daily and 10% of the patients presented a contraindication, with no difference between the two groups.
3.3. Weight gain

Weight gain was significant and similar in both groups, being steeper during the early months, and then much slower (baseline – 3 years for both groups together $P < 0.0001$, group A vs. group B $P = \text{ns}$, interaction not significant) (Fig. 2c).

3.4. Hypoglycaemia

During the 3 years follow-up, 14 severe hypoglycaemic events occurred in 10 patients, with no significant difference between the two groups. The mean frequency of minor hypoglycaemia was $1.3 \pm 2.3$ events per month per patient, with no significant difference between the two groups.

3.5. Safety

No acute hyperglycaemic episode related to catheter obstruction was observed.

3.5.1. Cardiovascular events

At the beginning of the study, the patients had high cardiovascular risk: 10 of them ($P \ A$ vs. $B$: NS) had history of cardiovascular disease, 39 ($P \ A$ vs. $B$: NS) were treated for arterial hypertension and 10 for dyslipidemia ($P \ A$ vs. $B$: NS). During the study, six patients, all in group $A$ (group $A$ vs. group $B$: $P < 0.03$) presented a cardiovascular event: two myocardial infarctions, one acute coronary syndrome, one coronary angioplasty, one acute coronary syndrome, one coronary angioplasty and one stroke.

3.6. Patient satisfaction

Analysis showed overall improvement of patients’ quality of life during the 3-year study period, with no difference between the two groups. Of 11 items assessed on SF36 questionnaire, four showed no change and seven significantly improved (limitations due to physical problems, perceived health, vitality, general mental health, limitations due to emotional problems, change in perceived health, overall psychological score). The impact score assessed by DQOL questionnaire (scale range 0 to –5) showed significant improvement: from $–2.37 \pm 0.51$ at baseline to $–2.19 \pm 0.43$ at the end of the study ($P = 0.0024$). Of three items assessed by DTSQ questionnaire, one showed no change (perceived frequency of hypoglycaemia) and two significantly improved: satisfaction with treatment (scale range 0–36) improved from $25 \pm 7$ at baseline to $28 \pm 6$ at the end of the study ($P = 0.0036$) and perceived frequency of hyperglycaemia (scale range 0 to –6) decreased from $–3.9 \pm 1.7$ to $–2.5 \pm 1.6$ at the end of the study ($P = 0.0001$).

4. Discussion–conclusions

In spite of good clinical practice recommendations for the treatment of type 2 diabetes, one third of type 2 diabetic patients in France [10] or in the United States [11] have a poor glycaemic control, assessed by HbA1c levels $>8\%$. Few studies have evaluated the interest of CSII in type 2 diabetes. Our study was designed to compare, in poorly controlled type 2 diabetic patients, the efficacy of two therapeutic associations combining OHA and CSII on HbA1c, hypoglycaemic episodes and quality of life. The originality of our study lies in the combination of OHA with CSII used with minimal self-use proce-
dures. Moreover, to our knowledge, it is the first long-term follow-up study (3 years) using CSII in type-2 diabetic patients.

At the beginning of the study, both groups have similar mean age and estimated mean duration of diabetes. Unfortunately, in spite of randomization procedure, patients in group A have significantly higher HbA1c and lower C-peptide levels. These discrepancies suggest that the disease had been progressing for a longer time in this group, confirming the difficulty of assessing with any accuracy the onset of type 2 diabetes.

Whatever the group, similar efficacy in terms of HbA1c was obtained, whether the optimization of insulin doses was exerted on basal rate or on boluses. CSII by external pump has proved its efficacy and safety in type 1 diabetes [2,3,6,12]. Our results in type 2 diabetes are similar to those of previous works with either smaller patient series or of shorter duration [7,8,13,14]. Three recent studies compared CSII and MDI in type 2 diabetic patients. Raskin et al. [7] obtained with a short-acting insulin analog administered by pump a 0.62% decrease of HbA1c after 24 weeks in 66 patients. In an older population, Herman et al. [8] report with CSII a drop of 1.7% in HbA1c after 1 year. In these two studies, baseline HbA1c was lower than in our patients, respectively, 8.2 and 8.4%. These studies conclude that CSII and MDI exert the same efficacy on HbA1c in the populations studied.

But Wainstein et al. [15] reported, in an 18-week study, a better HbA1c improvement with CSII than MDI in 40 obese patients (BMI > 30 kg/m²) with poor glycaemic control (HbA1c > 8.5%) in spite of MDI with high daily doses (1 U/kg per day).

After 6 months and 1 year of pump therapy, we obtained in our study a decrease of 1.7 and 1.6%, respectively, in HbA1c. This decrease is larger than in the study reported by Raskin and Wainstein but comparable to what is reported by Herman. However, the final results observed in this study are better than ours at 1 year (6.6 vs. 7.8%). This might be partly due to the fact that in this study the patients were provided with strong support and frequent calls, allowing to pursue tight control. In spite of a more usual follow-up, the improvement in HbA1c observed in our study was durable throughout the 3 years follow-up. To our knowledge, no other study evaluating the long-term effects of CSII in type 2 diabetes has yet been reported.

In spite of our strategy of follow-up and treatment adjustments, and although we achieved an HbA1c decrease of more than 1% at 3 years in both groups, we did not attain the objectives recommended by the French Recommendations [16] or the ADA [17]. Our results are nevertheless encouraging, as the UKPDS clearly showed that a 1% decrease of HbA1c level was associated with a significant 37% decrease of microvascular complications [18]. They might have been even better if we had used a short-acting insulin analog instead of rapid insulin, which was more commonly used when we started the study. Moreover, we question whether we would not have achieved a greater decrease of HbA1c level with a more intensive adjustment protocol.

The insulin doses used were lower than those generally reported in the literature. It is partly explained by our protocol limitation on one hand and perhaps by the association of OHA to insulin on another hand. After 1 year, the average dose required was half that used in the study reported by Herman et al. [8]. These doses increased over the 3-year period, confirming the beta-cell deterioration described in the UKPDS [19].

Weight gain is a matter of concern in type 2 diabetic patients treated by insulin. A 1% decrease in HbA1c is known to lead to a 2 kg weight gain in 1 year [20,21], which is about the same as that observed in our study. On this point, it is difficult to compare our findings with those of earlier studies combining insulin, sulfonylureas and metformin, as our study was of much longer duration than the previous ones and the mode of insulin administration was different. It is noteworthy that most of the excess weight was gained during the first year of treatment. Weight gain was similar in both groups, probably partially associated with HbA1c improvement. As metformin dosage was similar between the groups, we hypothesize that regarding weight gain, the higher sulfonylurea dosage in group B counteracted the effect of lower insulin doses in the same group.

The initial protocol was unsuccessful in 12 non-responder patients in whom a combined adjustment of basal rates and boluses was necessary to overcome, at least partly, the deficiency of insulin secretion and the intensity of insulin resistance attested by the higher weight and waist circumference. These patients had higher baseline HbA1c levels, insulin requirements, both fasting and postprandial glycaemic levels.

Severe hypoglycaemic episodes were more frequent than in other studies on intensified treatment of type 2 diabetes, notably the FINFAT study [22] or that of Okubo et al. [23], but comparable to what was observed in the longest study with CSII in type 2 diabetes yet reported [7]. These episodes occurred in 10 patients, independently of their group, and most were attributed by the patients to dietary errors.

In spite of high cardiovascular risk, these patients presented fewer cardiovascular events than could have been expected according to the results of the Veterans Study [24]. This is probably related to intensified management of the other risk factors (hypertension, dyslipidemia) and to the systematic prescription of platelet antiaggregants. We have no really satisfactory explanation for the fact that all cardiovascular events occurred in group A. We hypothesize that the greater glycaemic imbalance in this group at baseline may have played a role. Moreover, as discussed before, baseline C-peptide was significantly higher in group B, suggesting that the disease had been progressing for a shorter time in this group. Lastly, it is difficult to draw any firm conclusions concerning this dissimilarity because of the small number of patients in each group.

At a time when pump therapy becomes more widespread in France, we demonstrate, like other authors [7–9] that treatment...
by portable pump can easily be used on a routine basis in patients with type 2 diabetes. In 3 years, we observed no cases of acute hyperglycaemic episode requiring hospitalization, in spite of the expected occurrence of catheter obstruction, a technical complication, which is fairly frequent with pump treatment. This was already the case in previous studies.

None of the patients in our study had to be excluded because of inability to learn pump use. Only five patients switched from CSII to MDI, all after 18 months of CSII treatment. They chose MDI for psychological pump intolerance and not for the absence of efficacy.

Our results even suggest that the pump may be used by the patient with basic manipulations, without boluses (sulfonylureas being taken before each meal) and without modifying basal infusion rate between each visit, the patient only learning to fill the reservoir and catheter. This appears to indicate that pump use is possible even in poorly skilled patients. However, a tighter blood glucose control can be obtained when an intensified follow-up is implemented for highly functional patients [8].

Quality of life assessment showed improvement of both objective and subjective criteria, in physical and psychological dimensions. Patients were more satisfied with their treatment and the impact of the disease decreased. These results are consistent with previous reports [7]. After the completion of the 3-year study, all the patients but four chose to continue on pump therapy, which confirms the results of quality of life questionnaires and the good tolerance of the pump, even in the long-term, in patients with type 2 diabetes [25,26].

In conclusion, this work suggests that routine pump therapy in patients with type 2 diabetes, especially those with chronically inadequate glycaemic control, is both feasible and effective in the long-term. The combination of CSII with OHA could be a therapeutic solution for patients in whom conventional treatment has failed. Improved glycaemic control in these patients is accompanied by improved quality of life, reflecting the acceptability of pump therapy in this population.

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