Original article

Real-life application and validation of flexible intensive insulin-therapy algorithms in type 1 diabetes patients

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Abstract

Aims. – Flexible intensive insulin therapy (FIT) has become the reference standard in type 1 diabetes. Besides carbohydrate counting (CHO), it requires the use of algorithms to adjust prandial insulin doses to the number of CHO portions. As recourse to standard algorithms is usual when initiating FIT, the use of personalized algorithms would also allow more precise adjustments to be made. The aim of the present study was to validate personalized prandial algorithms for FIT as proposed by Howorka et al. in 1990.

Methods. – We conducted a 4-month observational study of 35 patients with type 1 diabetes, treated with FIT for at least 6 months, who were already using Howorka’s prandial algorithms (meal-related and correctional insulin doses for blood glucose increases induced by CHO). These patients were asked to use a personal digital assistant (PDA) phone with an electronic diary (instead of a paper one) to take advantage of the computerized data-collection system to assess the quality of postprandial metabolic control.

Results. – Whatever the number of CHO portions, mean postprandial blood glucose values remained close to the target of 7.8 mmol/L, and the compensatory algorithm allowed precise correction of preprandial hyperglycaemia. In fact, the algorithms for meal-related and correctional insulin doses at the end of the study did not differ significantly from those initially calculated, but they generally differed from one patient to another.

Conclusion. – In type 1 diabetic patients treated with FIT, the use of individualized parameters permits fast and accurate adjustment of mealtime insulin doses, leading to good control of the postprandial state.

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Keywords: Type 1 diabetes; Flexible intensive insulin therapy; Carbohydrates; Prandial insulin dose; Personalized algorithms

Résumé

Élaboration d’algorithmes pour l’insulinothérapie fonctionnelle et validation de ces algorithmes dans la vie courante.

Objectifs. – L’insulinothérapie fonctionnelle (IF) est devenue le traitement de référence du diabète de type 1. Outre le décompte des glucides, elle nécessite des algorithmes pour ajuster la dose d’insuline prandiale aux glucides. Si le recours à des algorithmes standards est classique lors du démarrage de l’IF, l’utilisation d’algorithmes personnalisés pourrait permettre des ajustements plus précis. L’objectif de notre étude était de valider les algorithmes personnalisés prandiaux d’IF proposés par Howorka et al.

Méthodes. – Nous avons conduit une étude d’observation de quatre mois chez 35 patients diabétiques de type 1, pratiquant l’IF depuis au moins six mois et utilisant déjà les algorithmes prandiaux d’Howorka (dose d’insuline liée au repas, dose d’insuline de correction, valeur hyperglycémiant de d’une portion de glucides). Il était demandé aux patients d’utiliser un PDA phone avec carnet électronique pour bénéficier du recueil des données. La qualité du contrôle glycémique postprandial a été évaluée.

Abbreviations: BG, Blood glucose; b.w., Body weight; CF, Correction factor; CHO, Carbohydrate; CSII, Continuous subcutaneous insulin infusion; FBG, Fasting blood glucose; L-FBG, Late fasting blood glucose; FIT, Flexible intensive insulin therapy; MDI, Multiple daily insulin injections; OGTT, Oral glucose tolerance test; PP, postprandial; PPBG, Postprandial blood glucose; TDD, Total daily insulin dose.

Parts of the present study were presented in abstract form at the ALFEDIAM Annual Congress, held in Marseille, France, on 22 March 2007.

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1 Clinical organization and follow-up of patients.

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1. Introduction

Intensive insulin treatment — represented by basal-prandial insulin regimens — is currently the best way to achieve strict glycaemic control of type 1 diabetes [1–3]. Such regimens use a long-acting insulin analogue to control FBG levels and a short-acting insulin analogue for postmeal glucose excursions (or a CSII system) to replace insulin in a way that closely approximates normal physiological patterns. Until recently, type 1 diabetic patients were expected to follow a rigid meal plan, with a controlled and often restricted CHO content, and stated meal-time insulin doses preadjusted to it. However, such fixed meal plans tend to be poorly accepted by most patients, who desire a "normal" lifestyle. For this reason, FIT was conceived to enable good control of diabetes without the need for meal planning and scheduled food intakes. Indeed, liberalization of food intake is made possible by meal-related insulin applications. Conversion to FIT simply requires that the patient accurately counts the CHO portions in each meal and uses simple algorithms to adjust meal-related insulin doses to the number of portions.

Several methods can determine the ratio of insulin units per CHO portion. In the global method, patients initiate treatment on the basis of mean and empirically estimated insulin doses [4–6]. However, the method used in the present study is based on individualized algorithms for FIT, first proposed by Howorka et al. [7]; and adjustment of their personalized algorithms with FIT results in good control of the postprandial state in type 1 diabetic patients.

2. Patients and methods

2.1. Patients

We recruited 35 consecutive patients attending the diabetes department of the Sud-Francilien Hospital. Prerequisites for inclusion were: willingness to participate in the study; clinical diagnosis of type 1 diabetes; duration of diabetes of more than 1 year; and use of the FIT strategy for at least 6 months. All patients were being treated by either CSII or MDI on entering the study. Also, at least 6 months before starting the study, all had taken a 5-day structured inpatients training programme on FIT, focusing on the following techniques: 20 g CHO portion counting; calculation of short-acting prandial insulin using Howorka’s algorithms [7] (Table 1); and adjustment of their prandial personalized algorithms to achieve a postprandial target of 7.8 mmol/L.

2.2. Methods

2.2.1. Patients’ follow-up

On entering the study, patients were taught how to use a PDA phone with an electronic diary application (instead of the usual paper logbook). The patients’ personalized algorithms for FIT were calculated by the medical team and programmed into their PDA phone. Before each meal, patients were asked to enter the meal-related insulin doses (the number of insulin units required to metabolize one CHO portion); correctional or compensatory insulin doses (the number of insulin units required to reduce blood glucose (BG) values by 5.55 mmol/L); BG increase induced by one CHO portion.

Personalization of these algorithms was achieved by formulas using the patients’ body weight and insulin sensitivity (Table 1). These algorithms could then also be further adjusted by patients according to their specific glycaemic prandial needs.

To validate these personalized algorithms for FIT, we conducted a 4-month observational study of 35 type 1 diabetic patients currently being treated with FIT for at least 6 months and already using the algorithms. These patients were asked to manage their diabetes as usual, but had to use a personal digital assistant (PDA) phone with an electronic (instead of paper) diary to allow complete and accurate collection of their data.

Table 1

<table>
<thead>
<tr>
<th>Howorka et al.'s [7] personalized algorithms for flexible insulin therapy adapted for 20 g carbohydrate (CHO) portions at mealtime.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prandial insulin and correction of abnormal blood glucose (BG) values</strong></td>
</tr>
<tr>
<td><strong>Insulin sensitivity coefficient ( k = ) theoretical basal+prandial insulin requirement / current total insulin requirement</strong></td>
</tr>
<tr>
<td>Theoretical basal insulin requirement = 0.35 U/kg body weight (b.w.)</td>
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<tr>
<td>Theoretical prandial insulin requirement = [average daily CHO (g/20) × 2.2]</td>
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<tr>
<td>P inual insulin and correction of abnormal blood glucose (BG) values</td>
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<tr>
<td>Insulin requirement for one 20 g CHO portion = 2.2 × ( K )</td>
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<tr>
<td>One unit extra short-acting-insulin BG-lowering effect: ( \Delta BG ) (mmol/L) = (–1.94 × 1/K × 60 kg b.w.)</td>
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<tr>
<td>( \Delta BG ) (mmol/L) = 4.44 × 60 kg b.w.</td>
</tr>
<tr>
<td>Basal insulin requirement = 0.35 U/kg b.w. × ( K )</td>
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</tbody>
</table>

An additional algorithm for protein/fat was proposed by Howorka et al. [7] for meals low in CHO: 0.45 U/100 kcal protein or fat × \( K \). However, patients are not being taught to use this in the current practice.

The present study objective was to confirm that the use of personalized algorithms with FIT results in good control of the postprandial state in type 1 diabetic patients.
value of their capillary BG and the number of 20 g CHO portions they intended to eat into the electronic logbook, which then automatically calculated the prandial short-acting insulin dose. This dose was reduced by 30 or 50% in case the patient planned to subsequently perform moderate or intense physical activity. Patients could accept or decline the device’s proposed calculation and, in the latter case, manually enter the insulin dose they intended to inject.

Self-monitoring of BG values was recommended to be done six times a day — before (FBG) and 2 h after the beginning of each meal (2h-PPBG) — and, occasionally, at around 0300 h (L-FBG) in the morning. The following parameters were recorded every day throughout the 4-month study: FBG, 2h-PPBG and L-FBG values; and the number of CHO portions and insulin units (meal-related and correctional insulin doses) at each meal. These data were transmitted via the PDA’s general packet radio service (GPRS) network to a secure website where they were collected for the analyses. In addition, the site allowed authorized caregivers to follow the patients’ results at all times, and to contact the patients by telephone to offer more information and advice.

2.3. Evaluation of Howorka’s algorithms for prandial insulin requirements

2.3.1. Meal-related insulin needs

Correlation between the number of CHO portions and the mean 2h-PPBG value was studied.

2.3.2. Correction of abnormal BG values

Three BG values were analyzed: the FBG before each meal; the 2h-PPBG; and the FBG before the next meal or the L-FBG (after the last meal of the day, or dinner).

2.3.3. Impact of meal protein content

BG values were assessed in four calibrated dinners that contained the same number of CHO portions and where the meal-related insulin dose was adjusted accordingly. The first, a ‘usual dinner’ previously defined by a diettitian, served as the reference and contained a determined ration of proteins; for the second dinner, patients were asked to consume no proteins; for the third and fourth dinners, patients were to eat a double ration of proteins. In addition, for the fourth dinner, extra insulin was added as per Howorka’s algorithm correction for protein/fat. For each dinner, the premeal, 2h-PPBG, nocturnal and following day’s FBG values were collected. Patients were asked not to drink any alcohol during this four-dinner test.

2.3.4. Metabolic control

Patients self-monitored their own BG, using glucometers that were validated for accuracy against the local laboratory reference method at each visit. Metabolic control was assessed by HbA1c, measured by high-performance chromatography. The upper reference range for those without diabetes was 6.1%. For each patient, the HbA1c value at the end of the study was compared with the baseline value.

2.3.5. Safety

The main safety criterion was the occurrence of hypoglycemic events. Major events were defined as those requiring external assistance, while minor events were defined as BG values < 3 mmol/L, according to the European Medicines Evaluation Agency (EMEA) classification. These events were all recorded in the electronic diary.

2.3.6. Statistical analysis

This was performed using Statistical Package for Social Sciences (SPSS), V14.0 and Excel 2003 software, and the results reported as means ± S.D. Paired Student’s t test was used for estimating significant differences vs baseline values (within-subject comparisons). Mean BG values were compared across different patient subgroups using analysis of variance (one-way ANOVA), and correlation tests of quantitative data were performed using Pearson’s coefficient.

3. Results

The mean study duration was 17 weeks (range: 5–25 weeks, median: 18 weeks), and followed 35 consecutive patients (23 men, 12 women) with type 1 diabetes of at least 1 year’s duration. Patients were 39.1 ± 10.8 years of age; their body mass index (BMI) was 25.1 ± 3.5 kg/m²; and their diabetes duration was 18.8 ± 11.1 years. The mean HbA1c was 7.8% at baseline. Fourteen patients were treated with CSII and 21 with an MDI regimen (glargin and lispro or aspart). Six patients dropped out because of technical problems (loss of the Med-passport Diabetes software in the temporary memory of the PDA phone) that no longer occur with more recent PDA models.

3.1. Mean glycaemic profiles

From these 35 patients, 5393 BG values were collected during the first month of the study (1072 observation days), comprising 3092 FBG or premeal BG values, 1931 2h-PPBG and 370 L-FBG values. The mean FBG value was 8.0 ± 3.6 mmol/L at breakfast, 7.3 ± 3.3 mmol/L at lunch and 8.5 ± 3.8 mmol/L at dinner. The means of individual BG excursions (2h-PPBG and FBG) were minimal and not relevant (+0.07 mmol/L at breakfast, +0.14 mmol/L at lunch and +0.06 mmol/L at dinner). Similar results were found during the last month of the study, with no differences in glycaemic profiles in patients using CSII compared with MDI. Also, whatever the preprandial values, the 2h-PPBG values remained close to the target of 7.8 mmol/L and were similar for all three meals.

3.2. Prandial insulin

3.2.1. Meal-related insulin

According to Howorka’s calculations, 2.3 ± 0.8 insulin units (U) were necessary to metabolize one 20 g CHO portion (P). At the end of the study, the mean ± S.D. prandial algorithm was 2.5 ± 1.2 U/P (range: 1.5–7) at breakfast, 2.4 ± 0.9 U/P (range:
Fig. 1. Whatever the number of 20 g carbohydrate (CHO) portions of the meal (from 0 to 7), the mean 2h-PPBG levels remained close to the target of 7.8 mmol/L. No relationship was found between the number of 20 g CHO portions and mean 2h-PPBG values. The vertical line marks the mean values of all episodes of postprandial glycaemia; n: number of meals.

1–4.5) at lunch and 2.4 ± 0.9 U/P (range: 1–4) at dinner. There were no statistically significant differences between the initial and final algorithms. However, meal-related insulin needs varied considerably from one individual to another, as reflected by analysis of the extremes.

The 2h-PPBG values were not influenced by the CHO in each meal (Fig. 1), as the insulin dose was adjusted according to the number of CHO portions. Also, whatever the number of CHO portions of the meal (from 0 to 7), the mean 2h-PPBG levels stayed close to the targeted value of 7.8 mmol/L. Control of PPBG values was particularly satisfactory for the 4.2% of meals that contained six or more CHO portions.

3.2.2. Correctional insulin use

Insulin compensation was widely used, as it was recommended as soon as premeal glycaemia exceeded 6.1 mmol/L and, by Howorka’s calculations, 3.8 ± 1.8 insulin units were necessary to reduce BG values by 5.55 mmol/L. There were no differences in mean correctional insulin doses at the end of the study vs baseline (3.4 ± 1.4 insulin units [range: 1–7] vs 3.5 ± 1.4 [range: 1–7]).

Specific analyses of correctional insulin use were performed using three measures of glycaemia classified according to the absence or presence of compensation and, in cases of compensation, according to the level of FBG (Fig. 2). In all cases, the 2h-PPBG remained close to the objective of 7.8 mmol/L. There were no relevant differences in mean 2h-PPBG or in subsequent FBG values whether patients with various levels of preprandial hyperglycaemia or in those who were already well equilibrated before meals.

Although the occurrence of mild hypoglycaemic episodes was slightly higher in patients with the highest mean levels of FBG (>16.7 mmol/L) compared with the other patient groups, the difference was not significant (6% vs 3–5% for PPBG values, and 8% vs 2–6% for the subsequent FBG values).

3.3. Flexible food intake

Did patients vary the CHO content of their meals from one day to the next? Indeed, patients were shown to generally enjoy dietary freedom. For lunch and dinner, patients consumed a similar CHO amount for about 50% of their meals. For 25% of their meals, they ate considerably less CHO (one to four portions less, or 20–80 g of CHO). For the remaining 25% of their meals, the CHO ration was usually increased (one to three portions more, or 20–60 g of CHO). At breakfast, the CHO portion was more regular: 65% had the fixed median ration, 24% had more and 11% had less.

3.4. Meal protein content and glycaemic control

Patients had four successive calibrated dinners (D1–D4) containing the same amount of CHO. The first had a standard amount of protein (D1: 40 ± 10 g), the second had effectively no protein (D2: 9 ± 6 g), and the last two had twice the amount of protein (D3/D4: 80 ± 21 g). Lipids increased accordingly from D2 (23 ± 8 g) to D3/D4 (77 ± 21 g), but the 2h-PPBG was similar whatever the protein content ($P = 0.57$; Fig. 3). However, FBG values the next morning were significantly different ($P = 0.001$), with FBG delta values of +1.22 mmol/L (FBG_D2−FBG_D1; $P = 0.03$) and +2.85 mmol/L (FBG_D3/D4−FBG_D2; $P < 0.001$). Comparison with the D1 dinner showed a small, non-significant increase in FBG value (FBG_D3/D4−FBG_D1: +1.6 mmol/L; $P = 0.6$). An additional insulin dose, as per Howorka’s correctional algorithm for protein/fat, failed to correct this FBG increase (D4 vs D3).
ner — but other algorithms have been proposed [4,6]. The doses — for example, 2 U/10 g CHO portion at breakfast, 1.5 mean and empirically estimated meal-related insulin rates of 2h-PPBG and L-FBG values were 47 and 33%, whole study population and > 90% in 20 cases. The mean record- ration of proteins; and (4) identical to the third dinner, but with extra insulin added according to Howorka’s algorithm for meals low in CHO. For each dinner, the FBG before the meal, 2h-PPBG, nocturnal BG (L-FBG) and FBG value the next day were collected.

3.5. Metabolic results

The mean HbA1c value was significantly lower at the end of the study than at the initial visit (7.3 ± 0.6% vs 7.8 ± 0.9%; P = 0.003).

3.6. Safety

No severe hypoglycaemic event was reported during the study. In fact, there was a trend towards a decrease over time in the number of mild hypoglycaemic episodes — from 1.4 hypoglycaemic events/individual/week at the initial visit to 0.8 such events at week 12 (R² = 0.19; P = 0.156).

3.7. The electronic diary system

The mean recording rate of fasting and preprandial daily data (BG values, CHO portions and insulin doses) was 90% for the whole study population and > 90% in 20 cases. The mean recording rates of 2h-PPBG and L-FBG values were 47 and 33%, respectively. There was no fall in use of the electronic diary throughout the study.

4. Discussion

Whatever the method, FIT requires CHO quantification, a rational system of insulin substitution and intensive patient training. Many physicians initiate prandial insulin administration based on mean and empirically estimated meal-related insulin doses — for example, 2 U/10 g CHO portion at breakfast, 1.5 U/10 g CHO portion at lunch and 1 U/10 g CHO portion at dinner [5] — but other algorithms have been proposed [4,6]. The use of standard algorithms initially appears to be easier and less time-consuming, but its validity has not been assessed until now; in fact, it may overestimate the need for meal-related insulin [8], and adjustments are often required to achieve suitable algorithms for a given patient. Another method estimates the mean CHO amount consumed over 24 h and reports it to half the total insulin daily dose (‘carbohydrate-to-insulin ratio’) [1,9]. In the present study using individualized algorithms, as elaborated by Howorka et al. [7], the patients’ mean meal-related insulin doses at the end of the study were similar to those initially calculated, suggesting that they were properly adjusted from the beginning. The wide range of values among the study population — from 0.5 to 7 U/P — highlights the importance of personalized algorithms using the patient’s weight and insulin sensitivity. There was a strong, linear correlation between the amount of CHO consumed and insulin dose, and a similar correlation between CHO and insulin delivery had previously been demonstrated with an artificial pancreas [10]. In the present study, whatever the number of CHO portions in the meal (ranging from 0 to 7), the mean 2h-PPBG levels remained close to the target of 7.8 mmol/L. The algorithm was particularly well adapted for meals with a high CHO content and, contrary to the usual advice [5], there was no need for additional insulin.

In cases of elevated preprandial glycaemia, correctional insulin was added to the meal-related dose. The algorithm of 1 U of insulin to reduce BG value from 0.30 to 0.50 g/L has been proposed [1,4,5]. The ‘1500 Rule’ has also been widely used, in which the hypoglycaemic power of 1 U of insulin is the ratio of 1500/TDD. However, its proponents have recently reevaluated this ‘rule’, using data from 182 type 1 diabetic patients treated with pump therapy whose diabetes was well equilibrated [11], and now recommend the formula CF = 1900/TDD (the ‘1900 Rule’).

Beside carbohydrate counting, this method takes little account of insulin sensitivity, which largely modulates insulin needs. However, thanks to the use of individualized parameters, the present study showed that the 2h-PPBG and subsequent FBG were close to target whatever the preprandial BG. Nevertheless, the hypoglycaemic power of 1 U of insulin varied by a coefficient of 10 between patients (from 0.1 to 1), supporting once again the case for personalized parameters.

Dietary freedom was widely enjoyed, as our patients did not consume the same mean CHO amounts in at least half the cases (± 20–80 g of their own median CHO ration). Also, the preservation of 2h-PPBG values at around 8.3 mmol/L in spite of such dietary freedom proves the validity of the algorithms used.

The four-dinner test was designed to assess the impact of the meal protein content on BG values. The four mean 2h-PPBG values did not differ, but an increase in FBG values the next day was observed for the two dinners with the highest protein contents. FBG values the next morning were significantly different, with increases of +1.2 mmol/L for one vs no ration of proteins, and of +2.8 mmol/L for two vs no ration of proteins, suggesting a delayed effect of proteins on BG values. Indeed, the impact of the meal protein content on BG values has been reported elsewhere [5,12]. Sachon [5] proposed the addition of 1 U of insulin per 20 g of protein. In the present study, the
addition of an extra compensatory insulin dose at dinner for proteins, as proposed by Howorka et al. [7], proved ineffective for correcting the increase in FBG the next morning. This suggests that higher nocturnal secondary basal rates in cases of CSII should be helpful. The impact of the evening meal protein content on nocturnal plasma glucose regulation may be due to protein-induced glucagon secretion [13] or to activation of hepatic neoglucogenesis by gluconeogenic amino acids. Lipid activities also cannot be excluded, as both meal lipid and protein contents increased; however, the published data have so far been conflicting [5,14,15].

Metabolic control improved during the study even though patients were already being treated with FIT before entering the study. A significant 0.51% reduction in HbA1c was observed at 3 months and, at the same time, the incidence of hypoglycaemic events progressively decreased, although the reduction was not significant. An improvement of HbA1c with a concomitant reduction in the incidence of hypoglycaemia has already been reported in several studies evaluating FIT [16,17], and confirms the efficacy of the method for metabolic control.

However, the limitations of the present study need to be addressed. The study focused on prandial insulin doses and was designed to assess the efficacy of our FIT method in the control of the postprandial state, whereas good control of the basal state remains a prerequisite for effective adjustment of prandial insulin. Also, our study was an open-label, single-centre study, involving only a small number of type 1 diabetic patients. Finally, as it was not a comparative study, there was no control group.

Nevertheless, our method of FIT, based on the use of individualized patients’ parameters, permitted fast and accurate adjustment of prandial insulin doses that resulted in good control of the postprandial state. In future, it would be of interest to compare such a personalized FIT method with more global methods in a controlled comparative trial.

5. Conflicts of interest

Pierre Leurent is the founder and chief executive officer of VOLUNTIS, the company that developed the software used in the study. He is also a manager and shareholder in the company. The other authors do not have any conflicts of interest.

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