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Long term feasibility of multiple daily injections with insulin pens in children and adolescents with diabetes

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Abstract. During a period of 17 months, 15 C-peptide negative insulin-dependent diabetic children (14 ± 4 years old) have used an injector pen (Novopen, Novo, France) to deliver soluble insulin before meals, in association with an insulin syringe for long-acting insulin administration at bedtime. Despite frequent daily insulin injections (4–5) and blood glucose determinations (3–4), long-term patient acceptability as well as cutaneous tolerance were excellent. Novopen was experienced as a progress (100%) which made a multiple injection regimen acceptable and provided an improvement in the quality of life (77%), as recorded by questionnaires answered at the end of the study. Twelve out of 15 patients chose to continue this treatment. No significant change in glycaemic control was observed in the group as a whole. An improvement in glycosylated haemoglobin (HbA 1c) was noticed only in the previously "poorly-controlled" children ($n = 8$) with initial HbA1c $> 7\%$. In this group HbA1c decreased from $8.4 \pm 1.8\%$ (mean $\pm$ SD), to $7.3 \pm 1.2\%$ ($P < 0.05$) within the first 6 months of Novopen therapy. No increment of hypoglycaemia frequency and mean daily insulin requirements was observed. No ketoacidotic episode was noticed during the study. In conclusion, in this group of diabetic children, no long term metabolic improvement was obtained, despite excellent acceptability of the multiple injection regimen with Novopen.

Key words: Children with IDDM – Multiple insulin injections – Insulin injector pen – Blood glucose control

Introduction

Insulin delivery methods acceptable both to diabetic children and able to improve their glycaemic control are an important concern in paediatric practice. Children with insulin-dependent diabetes mellitus (IDDM) are especially prone to diabetic microvascular complications which are related to the duration of the disease and to the long-term quality of glycaemic control [9, 18]. Continuous subcutaneous insulin infusion (CSII) and multiple subcutaneous insulin injections (MSII) represent recent insulin regimens which are able to provide better metabolic control than conventional treatment. These regimens simulate the pattern of physiological insulin secretion, as previously shown by Rizza et al. in a short-term study [13]. CSII has proved to be efficient in glycaemic control in both children and adolescents with IDDM [3, 5, 6, 10]; however, its use is limited by either technical or psychological drawbacks or economic concerns (high cost, extensive involvement of the medical team). The MSII regimen has been shown to provide better glycaemic control than conventional therapy in clinical trials [4, 15]. A new device, the insulin injector pen [2, 11], a simple and attractive tool, is now likely to make the MSII regimens easier. We studied the use of insulin pens in children with IDDM to assess the long-term acceptability of MSII, the insulin delivery rules, and the impact on glycaemic control of this treatment.

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Abbreviations: CBG = capillary blood glucose; CSII = continuous subcutaneous insulin infusion; HbA1c = glycosylated haemoglobin; IDDM = insulin-dependent diabetes mellitus; MSII = multiple subcutaneous insulin injections

Patients and methods

Patients

Fifteen children and adolescents (7 girls and 8 boys) with a mean age of 14 years (range 5–19.5 years), with IDDM duration of 6 years (1–14 years) and C-peptide negative (evaluation by glucagon stimulation test) participated in the study (Table 1). They all had been previously treated with two daily injections of a mixture of insulins, adjusted on 2–3 daily capillary blood and urine glucose determinations. The protocol was proposed to children and adolescents who regularly attended our out-patient clinic, and were thought to be interested in improving glycaemic control or using a therapeutic scheme more compatible with their life style (adolescents). We excluded from the study patients with unstable psychological profiles or major family problems.

Methods

Insulin therapy protocol. The insulin pen used, Novopen is describe elsewhere [2]. Regular insulin (Actrapid HM, Novo, France) was given with the Novopen 20–30 minutes before each meal (3 to 4 meals a day). Long-acting insulin (Ultratard HM, Novo, France) was injected separately at bedtime using a conventional syringe. The starting dose of Ultratard was approximately 50% of the total dose on the conventional regi-

Table 1. Patients' data at entry into study

Patient	Sex	Age (years)	Duration of IDDM (years)	Insulin dose U/kg/day	Initial HbA1c (%)
1	M	14	4.5	1	7.6
2	M	12.2	4.5	0.9	5.9
3	F	14	5.5	0.8	7.6
4	F	18	13	0.9	7.2
5	F	5	4	1	7.6
6	F	17	2	0.6	5.9
7	M	12.8	4	0.7	5.6
8	M	19.5	5	0.7	4.9
9	M	8	4	0.7	7
10	F	9	1	0.6	7.6
11	M	18.4	9	0.9	6.9
12	F	16.7	4	0.9	13
13	M	16.5	10.5	0.9	7.9
14	M	18	14	1.1	8.8
15	F	11	6	1.2	6.3

men. The remainder was divided into preprandial soluble insulin doses.

Diet. Patients followed their usual diabetic diet which consisted of 50% carbohydrate, 15% protein and 35% fat given as 3 main meals (breakfast, lunch, dinner), without the usual morning snack. The optional afternoon snack was preceded by an injection of regular insulin.

Monitoring. Patients were instructed to measure and record capillary blood glucose (CBG) at fasting and just before administering the premeal injection; glycosuria and ketonuria determinations were made at fasting and before dinner. Patients attended our out-patient paediatric clinic once every 3 months. Weight, height and lipodystrophy evaluations were taken at each visit. Record books were kept to analyse the glycaemic control and hypoglycaemic episodes. Hypoglycaemia was graded as biological (CBG < 60 mg/dl with no symptoms), moderate (mild to moderate symptoms requiring carbohydrate intake by patients) or severe (loss of consciousness requiring the help of a second person).

Insulin dose management. Regular insulin doses were administered according to a sliding scale. The scale was based on pre- and postprandial CBG determinations during the initial hospitalization, and was regularly revised according to self-monitoring data. Ultratard doses were adjusted based on the mean fasting blood glucose and urine results.

Patient opinion. Following completion of the study, all patients answered a questionnaire focusing on technical aspects of the insulin pen and multiple injection regimen, and questions related to their life styles under this treatment. Personal opinions on the treatment were also sollicited.

Laboratory methods. Glycosylated haemoglobin (HbA1c) was measured by high performance liquid chromatography; normal values are $4 \pm 0.35\%$ (mean $\pm$ SD).

Statistical analyses. Data are expressed as mean $\pm$ SD (or SEM when indicated). Student's paired t test was used for the comparison of HbA1c values.

Results

Acceptability

The average MSII treatment duration was 17 months (range 6–24 months). Three patients discontinued the treatment after 6 months and went back to their conventional therapy, (one patient left the country, another found the insulin injections too frequent, and one adolescent failed to achieve improvement in glycaemic control). Twelve children out of 15 reached 18 months of MSII with Novopen and were willing to continue with this treatment.

Analysis of the patient questionnaire indicated a number of advantages of the Novopen and of a multiple injection regimen. The Novopen was considered to be convenient and easy to use by all patients; its conception and design made it easy to carry and could be used with discretion. All of them experienced the Novopen as a progress in therapy. The multiple injection scheme was found to be simple and the dosage adjustment easy to understand (100%). An improvement in the quality of life ("more freedom, less constraints, more flexibility of daily life") was reported by 77% of the patients. The need for 4 daily injections was described as a major disadvantage by 3 patients only. One patient discontinued the treatment for this reason in spite of an improvement of metabolic control. Technical aspects of the Novopen were described by the patients and 30% of the patients found injections to be less painful. Twelve patients followed the instructions and changed the needle every day, while 3 others changed it only twice a week. Three patients found the pen too heavy. The lack of vizualisation of the injected dose with Novopen was reported by three patients and could possibly result in mistakes in the insulin dose.

Cutaneous tolerance

The cutaneous tolerance was good. No local infections were found at the injection sites. Frequent examinations showed no higher frequency of lipodystrophy than with the usual twice daily injections.

Insulin requirements and weight

The mean daily insulin dose, expressed in units per kg, was 0.86 ± 0.17 (range 0.6–1.2) at the start of the study and did not vary during treatment (Table 2). The daily insulin dose distribution was stabilized at the end of the first 3 months of treatment for all patients and did not change thereafter. Of the total daily dosage $45 \pm 10\%$ was given at bedtime (Ultratard), $20 \pm 5\%$ before breakfast and dinner, $15 \pm 5\%$ before lunch (Actrapid). When a snack was eaten in the afternoon, $10 \pm 2\%$ of the total daily dose was given with the Novopen; this in turn diminished the percentage of the other daily insulin doses. No significant weight changes were observed during the study. Average excess weight, related to height and expressed in standard deviation (SD), was analysed: $+0.27$ SD at the start of the study, $+0.30$, $+0.14$, and $+0.28$ SD at 6, 12, and 18 months, respectively.

Metabolic control

The time course of HbA1c values is shown in Fig. 1. Mean HbA1c at the onset of the trial was $7.3 \pm 1.8\%$ in the entire group. This value did not change significantly during the 18

Table 2. Insulin requirements (mean ± SD) and frequency of hypoglycaemic episodes per patient and per month during the study: Hypoglycaemia was graded as biological when CBG was <60 mg/dl with no symptoms, moderate when mild and moderate symptoms required carbohydrate intake by patients. One severe hypoglycaemia occurred in one patient during the study

	Months			
	0	6	12	18
Insulin requirements (U/kg/day)	0.86 ± 0.17	0.86 ± 0.17	0.90 ± 0.16	0.82 ± 0.13
Hypoglycaemia				
Biological	7.5	6.8	5.5	5
Moderate	3	2	4	4

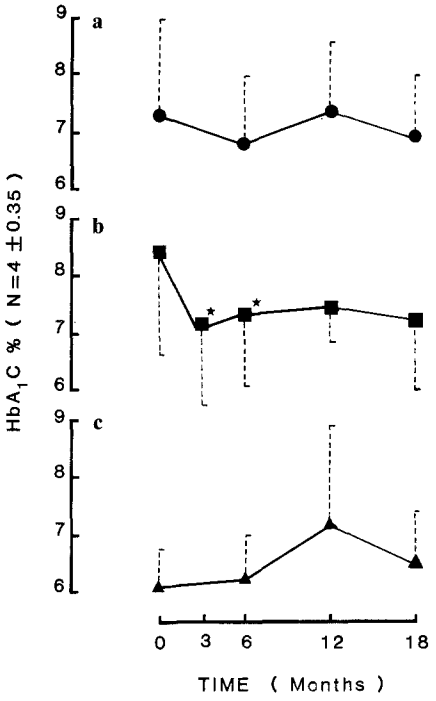

Fig. 1. Time course of glycosylated haemoglobin (HbA1c) in children and adolescents during the study period: this graph concerns the entire group but 15 patients completed the study for the first 6 months only. **a** shows the results (mean ± SD) for the whole group ($n = 15$); **b** shows the results for the group ($n = 8$) in whom basal HbA1c was >7%; **c** shows the results for the group ($n = 7$) in whom basal HbA1c was <7%. *$P < 0.05$ versus basal value

months of treatment. Data were further analysed according to a "cut off point" of HbA1c of 7%. A first group of children with poor control ($n = 8$; HbA1c = 8.4 ± 1.8% at the start of the study) exhibited an improvement in glycaemic control within the first 6 months of treatment (HbA1c = 7.3 ± 1.2%). The previously fairly well-controlled group ($n = 7$; initial HbA1c = 6.1 ± 0.7%) showed no significant changes in glycaemic control.

Hypoglycaemia

As shown in Table 2, there was no increase in the frequency of biological and moderate hypoglycaemia. One severe hypoglycaemic episode occurred in one patient. This episode was explained by intensive physical exercise following insufficient carbohydrate intake.

Hyperglycaemic episodes with ketonuria

An average frequency of two episodes of hyperglycaemia per patient per month (CBG > 250 mg/dl with glycosuria and moderate ketonuria) was observed. The episodes disappeared quickly after the injection of the higher soluble insulin dose recommended on the sliding scale. Serious episodes of diabetic ketosis did not occur under MSII treatment with Novopen.

Discussion

This study shows that the multiple insulin injection regimen with an injector pen is feasible on a long-term basis in diabetic children or adolescents. Fifteen patients adhered to this treatment for 17 months on average while 3 discontinued the treatment during the study. After the completion of the study, 12 subjects chose to continue this therapy. Despite the number of daily injections (4–5) all of them found the injector pen to be an improvement.

The regimen of split insulin doses increased the flexibility in the overall treatment of diabetes and thus improved the quality of life (well-being). The injections were made easier and more convenient through the use of the injector pen. These advantages have already been described in short-term studies in adults [2, 17] and adolescents with IDDM [1, 8], but the long-term acceptance of multiple daily injections by children was surprising and so far has not been documented. The patients have been quite compliant with various injections and home monitoring, as already described in a group of selected adolescents or children under different types of intensified treatment [15].

We found the multiple insulin injection regimen with a sliding scale to be important for patient education. The use of a sliding scale facilitates the adjustment of insulin doses. It enables the patient to understand more clearly the relationship between blood glucose determination and insulin dosage, and in some cases a better adherence to blood glucose monitoring. The same was true for CSII [10]. The children regarded the pen treatment as their own choice and became responsible for it.

Potential disadvantages of intensified treatment, such as increased hypoglycaemia and lipodystrophies were not observed in our study. They were avoided by an adapted educational program by a specialized team. Despite the surprisingly long and high adherence to this new treatment, no improvement of glycaemic control was demonstrated in the group as a whole during the 17 months of the study. Some reasons may be linked to the type of treatment itself. Although Ultratard is reportedly a long-acting insulin (24 h or longer) [7], its kinetics have not been precisely studied in children. Based on the results of the fasting urine and blood tests, we found Ultratard to be poorly reproducible in its action from one day to the next. This is in keeping with observations about variable individual plasma insulin concentrations after chronic administration of long acting insulin [14].

The lack of visual control fo the injected dose with the injector pen may be responsible for some hyperglycaemic episodes. In addition to these technical points, there are obvi-

ously a number of reasons related to patient behaviour that can play a role in the lack of improvement of glycaemic control.

Sliding insulin scales and frequent home blood glucose monitoring do not necessarily mean adequate insulin dosage adjustments. This phenomenon is already known in adults [16] but so far has been poorly analysed in diabetic children. Although we did not observe weight gains, we had no rigorous method to measure exact diet compliance. Poor eating habits are obviously responsible for a number of hyperglycaemic episodes in this age range.

This study calls for the need to describe and quantify the different familial, social, emotional and psychological factors which interfere with the treatment of diabetes in children and adolescents. Despite a sophisticated method of treatment, only a few of these apparently motivated patients could reach a mean normal level of HbA1c. Only the subgroup of previously poorly treated patients exhibited an improvement in metabolic status. Motivation for enrollment in the study and the advantage of the split doses of regular insulin may account for these improvements [12, 16]. This treatment represents a choise of insulin regimens for teenagers and adolescents with IDDM. It is safe and easy to use, when used by well-educated patients and monitored under the supervision of a specialized team. It provides the children with a degree of comfort and well-being considered to be important with respect to the burden of diabetes treatment in daily life. This multi-injection scheme with an injector pen can be offered to motivated patients who have reasonable familial support and adequate medical care. Whether this will represent a real improvement of glycaemic control on a long-term basis, and therefore on chronic complications of diabetes remain to be determined. Multiple injections are rendered easier by new tools. Our results demonstrate that insulinotherapy is one piece of a complex puzzle represented by the treatment of diabetes in childhood.

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