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Effect of nicotinamide therapy upon B-cell function in newly diagnosed Type 1 (insulin-dependent) diabetic patients

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Summary. This study describes the effects of nicotinamide therapy on B-cell function in Type 1 (insulin-dependent) diabetes. C-peptide secretion was studied in 20 patients newly diagnosed with Type 1 diabetes at basal state and also after an i.v. glucagon stimulus. Patients were randomly allocated according to a single-blind schedule, to one of the following treatments over a 45-day period: Group 1: 10 patients, nicotinamide 1 g/day; Group 2: 10 patients, placebo. The C-peptide secretion tests were performed before treatment and on days 15, 45, 180, 365 of the follow-up. The clinical and metabolic data were similar in the two groups of patients. Basal and stimulated C-peptide levels increased by 45 days in both groups, but the increase in stimulated C-peptide response was greater in the nicotinamide group ($p<0.01$). However, the B-cell function decreased after the period of nicotinamide administration. No difference in the number of clinical remissions or insulin requirement and HbA_1 between the groups was observed. These data suggest that treatment of Type 1 diabetes with nicotinamide at diagnosis is associated with a moderate increase of C-peptide secretion recovery.

Key words: Type 1 (insulin-dependent) diabetes mellitus, nicotinamide treatment, B cell function.

Several facts indicate that autoimmune mechanisms may play a role in the aetiology of Type 1 (insulin-dependent) diabetes [1]. This concept has led many authors to try various immunomodulating treatments at the onset of the disease [2–4]. No definitive conclusions have been reached, although Cyclosporin has yielded promising results in diabetic patients [2]. On the other hand, reports in animal studies state that nicotinamide, an inhibitor of the enzyme poly-(ADP-ribose) synthetase, prevents spontaneous diabetes mellitus in non-obese diabetic mice [5], and the induction of diabetes by streptozotocin [6], and may also induce islet B-cell regeneration [7]. In addition, recently Vague et al. [8] found a more frequent and sustained remission in Type 1 diabetic patients treated with nicotinamide.

On the basis that an autoimmune process is in progress at the onset of diabetes [9], and that nicotinamide could inhibit poly-(ADP-ribose synthetase) and NAD consumption, and improve insulin-synthesis [5, 6], we decided on the present study in order to evaluate the efficacy of nicotinamide on residual B-cell function in patients with Type 1 diabetes.

Subjects, materials and methods

The group studied included 20 newly diagnosed Type 1 diabetic patients classified according to the National Diabetes Data Group [10]. All the patients were admitted to hospital at the time of diagnosis and followed-up at the outpatient clinic 1 month after discharge and every 3 months thereafter. A specific diet comprising 55% carbohydrate, 35% fat and 15% protein, and two injections of intermediate highly purified porcine insulin (Insulatard, Nordisk, Gentofte, Denmark), supplemented by injections of regular insulin (Velosulin, Nordisk) when required, were prescribed. Patients were carefully instructed on home blood glucose self-monitoring.

One week after hospital admission, all patients were randomly allocated, according to a single-blind schedule, to one of the following oral treatments: A) Nicotinamide (Lacer Laboratories, Barcelona, Spain) (10 patients), 1 g/day; B) Placebo (10 patients). The treatments lasted 45 days.

In order to assess the B-cell function, a glucagon C-peptide test was performed in both groups of patients. B-cell function was measured on the day of discharge from hospital, before treatment with nicotinamide or placebo was started, and on days 15, 45, 180, 365 of the follow-up. The glucagon test was performed as follows: before morning insulin administration, fasting venous samples were drawn at basal state and 2, 4, 6, 8, 10 min after i.v. injection of 1 mg of porcine glucagon (Novo, Copenhagen, Denmark).

Plasma C-peptide (CPR) was determined by radioimmunoassay after plasma extraction with ethanol 96% [11]. The lower detection limit was 0.1 ng/ml. The intra- and interassay variation coefficients were 5.5% and 11.8%, respectively. C-peptide response (ng/ml 10 min) was derived from the area under the time curve for CPR values.

Islet cell antibodies (ICA) were determined in all the sera by indirect immunofluorescence on cryostat sections of a human donor pancreas (group 0), with serum obtained from the patient [12]. Blood glucose was analysed by a glucose-oxidase method adapted for Autoanalyser II (Beckman Instruments, Calif, USA) [13] and HbA_1 by ion-exchange chromatography (normal range: 5.5–7.1) [14].

Remission was defined as fasting plasma glucose below 7.8 mmol/l, postprandial glucose below 9 mmol/l, and HbA_1 below 7.5% in the absence of insulin or sulphonylurea treatment. Partial re-

Table 1. Clinical and metabolic data of subjects included in the study

	Patients treated with nicotinamide	Patients treated with placebo
Age (years)[a]	18.3 ± 6.7	15.5 ± 5.5
Sex (M/F)	5/5	8/2
Duration of diabetes[a] (days)	60.5 ± 45.3	74.5 ± 86.7
Ketosis	10	10
Ketoacidosis	1	2
Fasting glucose[a] (mmol/l)	17.3 ± 3.0	18.1 ± 5.1
HbA_1 (%)[a]	11.6 ± 1.8	12.0 ± 1.5
Fasting C-Peptide[a] (ng/ml)	0.57 ± 0.29	0.65 ± 0.20
ICA-IgG positives	6	7
CF-ICA positives	5	4
Thyroid Microsomal Abs	1	0
Thyroglobulin Abs	1	0
Gastric parietal cell Abs	2	2
Suprarenal Abs	0	0

[a] Results expressed as mean ± SD

Table 2. Basal plasma C-peptide values (ng/ml) (x ± SD), from patients treated with nicotinamide or placebo

	Nicotinamide group	Placebo group
At onset	0.568 ± 0.29	0.655 ± 0.20
At 15 days	0.851 ± 0.39	0.803 ± 0.32
At 45 days	0.818 ± 0.45	0.823 ± 0.41
At 180 days	0.731 ± 0.48	0.729 ± 0.34
At 365 days	0.580 ± 0.41	0.440 ± 0.21

mission was considered when this metabolic control was obtained with an insulin requirement of less than 0.5 IU kg body weight.

Statistical analysis

The significance of differences between group means was evaluated by a non-parametric statistical test (Mann-Whitney). Results are expressed as mean ± SEM and $p < 0.05$ was considered statistically significant. The study was approved by the Ethics Committee of Hospital Clinic, and informed consent was obtained from all patients.

Results

The characteristics of the subjects are presented in Table 1. There were no major differences between the groups for age, duration of diabetes, fasting glucose, HbA_1, and basal C-peptide. ICA were detected in 60% of the nicotinamide group and 70% of the placebo group, prior to initation of therapy. Initial titres of these antibodies were comparable between both groups. No differences were observed in the rate of decline (results not shown).

Subjects treated with or without nicotinamide showed similar C-peptide values at diagnosis (Table 2).

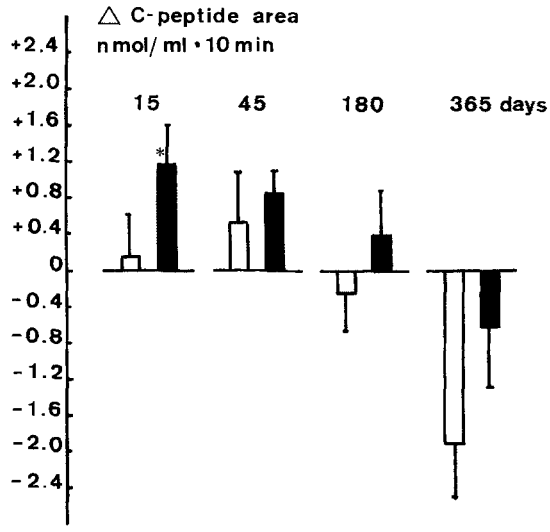

Fig. 1. Effect of treatment with nicotinamide (1 g/day) shaded columns) or placebo (open columns) on the incremental area under the C-peptide curve obtained after the i.v. injection of 1 mg of glucagon. Nicotinamide and placebo were withdrawn at 45 days. Results (mean ± SEM) are expressed as Δ in relation to the values of the first test (at diagnosis). * $p < 0.01$

Basal and stimulated C-peptide levels increased by 45 days in both groups (Table 2) and (Fig. 1). However, the increase in stimulated C-peptide response was significantly ($p < 0.01$) greater in the nicotinamide group (Fig. 1).

One patient treated with nicotinamide had discontinued insulin therapy for 90 days. Two patients from each group showed a partial remission. No differences in insulin requirement or HbA_1 between groups were observed. When physical, biochemical and haematologic parameters were considered no adverse effects of nicotinamide therapy were observed.

Discussion

Nicotinamide has been used therapeutically in several animal models of diabetes mellitus [5, 6, 15], on the basis that this drug inhibits nuclear poly-(ADP-ribose) synthetase. Activation of this enzyme has been implicated in the DNA repair, using cytosolic NAD as a substrate, and it is thought that the lowered concentrations of NAD may be the final step in the destruction of the B-cell [16, 17]. The possibility of preventing islet degeneration and restoring the B-cell function in Type 1 diabetes using nicotinamide or an other inhibitor of poly-(ADP-ribose) synthetase still remains.

In the present study, all the patients improved their B-cell function after the start of insulin treatment. However, nicotinamide administration enhanced insulin secretion recovery in diabetic patients. Yet, this effect was transient, as decreasing B-cell function was found after the period of drug administration. This limited degree of B-cell recovery in patients treated

with nicotinamide is also reflected functionally by the lack of evident changes in the degree of metabolic control.

A limited effect of nicotinamide treatment has also been observed by Vague et al. [8]. These authors found that in nicotinamide-treated diabetic patients the mean dose of insulin was lower, and a higher number of remissions was observed than in patients treated with the placebo. They concluded that the nicotinamide slows down destruction of B-cells and enhances their regeneration, but they do not provide hormonal data in support of this conclusion.

In our study, nicotinamide fails to modify the number of remissions and mean insulin requirements. The differences could be explained by variations of methodology or study design. Vague et al. used high doses of nicotinamide (3 g daily) during a 6-month period. In this sense it could be argued that in our study the treatment period is very short, but possible adverse effects of nicotinamide (i.e. insulinoma) were considered [18].

In conclusion, although no side effects were found, the recovery of B-cell function is little influenced by nicotinamide administration, so we do not recommend nicotinamide as a routine treatment at the onset of Type 1 diabetes. However, the effects could be considered promising, enough to warrant further studies.

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