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Prevention or delay of Type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide

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Summary. A controlled trial of oral nicotinamide to prevent the onset of diabetes mellitus in high risk children was conducted in two centres. The selection criteria were age less than 16 years, islet cell antibody ≥ 80 IUs, and first phase insulin release < 5th percentile. All of eight untreated control subjects have developed diabetes, whereas only 1 of 14 treated children has diabetes to date. This data suggests that nicotinamide has an effect in preventing Type 1 (insulin-dependent) diabetes and that randomized controlled studies are now indicated.

Key words: Nicotinamide, Type 1 (insulin-dependent diabetes mellitus, pre-Type 1 diabetes, islet-cell antibody, intravenous glucose tolerance test.

The onset of Type 1 (insulin-dependent) diabetes mellitus is preceded for many years by the appearance of islet cell antibodies (ICA) [1–4]. High levels of ICA in first degree relatives are followed inevitably by diabetes [2]. In the progression towards diabetes, first phase insulin release (FPIR) is progressively impaired and is a measure of progressive loss of pancreatic islet Beta-cell function [4, 5].

Nicotinamide has been shown to prevent diabetes in a non-obese-diabetes (NOD) strain of mice when given by injection [6] or in the diet [7], but is less effective in reversing the disease when given after hyperglycaemia is present [6]. It is not effective in preventing diabetes in the Bio Breeding (BB) rat [8]. The latter appears to apply when nicotinamide is used after the clinical onset of Type 1 diabetes in humans [9–11], particularly in children where it has not been helpful [12]. We therefore decided to study the effects of nicotinamide on a group of children who were first degree relatives of subjects with Type 1 diabetes, deemed at high risk of developing diabetes because of the presence of high levels of ICA and impaired FPIR.

Subjects and methods

Subjects

In Denver, 562 children (< 16 years of age) who were first degree relatives of subjects with Type 1 diabetes were screened for ICA. All children with ICAs were further selected by the presence of ICA levels of 80 or more IUs and impaired FPIR that were < 5th percentile (< 67 mU/l[5]). Those whose HbA_1 levels were initially elevated beyond the normal range were excluded. Insulin autoantibodies (IAA) were measured initially in most subjects. The first consecutive eight subjects meeting these criteria were not treated so that the natural history of the evolution of clinical diabetes could be studied. All eight were of Anglo descent and are a part of the Denver family study [4, 13]. Where possible, FPIR was then measured at least annually. Subsequent children were similarly studied, but treated with nicotinamide (see below). In the treated group (Table 1), subject 12 was of half-Hispanic/half-Anglo descent and subject 8 was of half-Oriental/half-Anglo descent. All other Denver subjects were of Anglo background.

In Auckland, all children ($n = 10$) were selected from a group of 1500 first degree relatives studied as above, using the identical selection criteria as in Denver, i.e. age less than 16 years, ICA ≥ 80 IU, and FPIR < 5th percentile. All Auckland children were of Anglo descent.

All of the treated children from both sites were treated with oral nicotinamide (150–300 mg · year of age^{-1} · day^{-1} with a maximum dose of 3.0 g/day using a slow release preparation; Innovite; Tigard, Ore., USA) given twice a day. The period of treatment (Table 1) was uninterrupted in all cases. Subjects were followed-up with repeated measurements of FPIR as above.

Methods

Islet cell antibodies were determined by an indirect immunofluorescence technique in Denver [4] and by a modification of this technique in Auckland [14]. Both laboratories participate in the International ICA proficiency programme and have validity, consistency, sensitivity and specificity of > 95% at all levels

Table 1. a) Untreated group

	Age years	ICA (IU)	FPIR mu/l	IAA (μU/l)	Time to diabetes (months)	FPIR at 1 year	FPIR at 2 year
	5	>80	39	–	4	–	–
	6	>80	35	964	21	–	–
	15	>80	47	158	11	–	–
	7	>80	43	237	57	61	56
	4	>80	29	60	14	3.5	–
	13	>80	15	0	3	–	–
	15	>80	37	20	21	–	–
	6	>80	4	30	4	–	–
Mean (range)	8.9	>80 –	31 (4–47)	– (0–964)	17 (3–57)	–	–

b) *Treated group.*

Subject number	Age	ICA	FPIR	IAA	Duration of treatment	FPIR at 1 year	FPIR at 2 year
1	8	320	66	14	30	83	–
2	1	80	44	176	12	–	–
3	3	80	47	3	27	79	128
4	5	160	56	40	26	98	72
5	4	160	12	92	24	32	–
6	6	80	15	18	17	14	–
7	8	160	39	6	13	–	–
8	6	1280	43	15	11	–	–
9	10	160	14	24	2	–	–
10	2	320	26	64	5	–	–
11	12[b]	>80	24	119	26	35	24
12	8[b]	>80	21	229	18	18	–
13	6[b]	160	27	–	6	–	–
14	10[a, b]	>80	3	137	24	0	7[a]
Mean (range)	6.3 (1–12)	>80 –	31 (3–66)	– (3–229)	17 (2–30)	–	–

[a] developed diabetes in 25th month; [b] treated subjects from Denver

ICA = islet cell antibodies; FPIR = first phase insulin response; IAA = insulin autoantibody

and of 100% at levels of 80 IUs. Thus, the two methods are comparable.

First phase insulin release was conducted in both centres as follows: dextrose, 0.5 g/kg body weight, was injected intravenously over 2–3 min and blood drawn for serum glucose and insulin levels before the injection and at precisely one and three min after completing the dextrose infusion. The sum of these two insulin levels minus the fasting level gives the FPIR.

The insulin assay was standardized between the two laboratories and thus the selection level (< 67 mu/l) was comparable.

IAAs were measured as described by Ziegler et al. [15] and standardized to the Boston method by serum exchange (courtesy Dr. G. Eisenbarth, Joslin Clinic, Boston, Mass., USA). Levels > 39 μU/l are considered abnormal [15].

Both centres had approval from their relevant human subjects ethical committees for this study.

Statistical analysis

Life table analysis was determined by the method of Cox and Oaken [16], with statistical significance determined by the Log Rank test, the Wilcoxon test, and the Likelihood Ratio test.

Results

The data for the two groups, untreated ($n = 8$) and nicotinamide-treated ($n = 14$) for age, initial ICA, FPIR, and IAA are shown in Table 1. Of the individuals completing 1 year of follow-up, four of eight in the untreated and none of nine in the treated group developed diabetes ($p < 0.03$; Fisher Exact test). Of those completing 2 years of follow-up, seven of eight in the untreated and none of six in the treated group had developed diabetes ($p < 0.002$; Fisher Exact test). Beyond that time, one of the 14 treated individuals has developed diabetes, and the last of the untreated group has done so. Thus, eight of eight in the untreated group and 1 of 14 in the treated group have the disease ($p < 0.00004$; Fisher Exact test). The mean time for the development of diabetes in the untreated group was 17 months. In contrast, none of the treated subjects had developed diabetes after the mean treatment period of 17 months.

Significant differences were found between the untreated and the treated groups (Fig. 1) in the life-table analysis ($p < 0.001$) using a Log-Rank test [16]. Other tests (the Wilcoxon and the Likelihood Ratio test [16]) confirmed a similar level of significance.

The one treated individual who developed diabetes in the 25th month after commencing treatment had the lowest initial FPIR (3 mU/l) found in both groups. In the treated group the FPIR 1 year after starting nicotinamide correlated with the initial response, with an overall improvement most marked in those with the higher initial response (Table 1).

Discussion

Nicotinamide has been shown to be effective in diminishing the occurrence of clinical diabetes in the pre-diabetic female NOD mouse, where the Beta-cell destructive process is assumed to be autoimmune [6, 7]. Nicotinamide

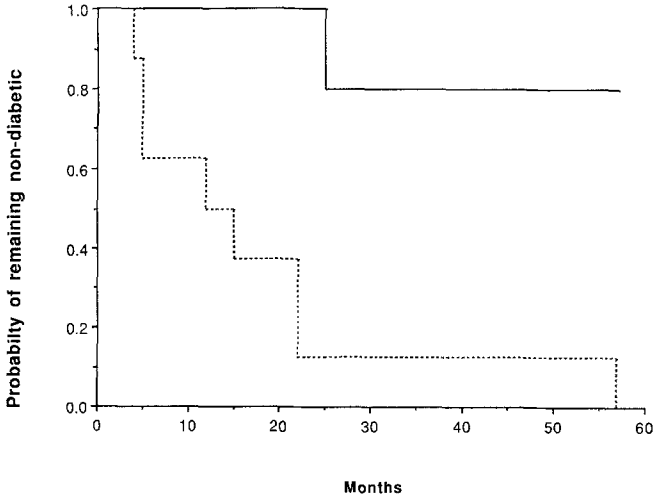

Fig. 1. Product limit survival estimates for control (------) and nicotinamide-treated (—) groups. Results were significantly different at $p < 0.001$ using the Log Rank, Wilcoxon or Likelihood Ratio tests [16]

inhibits poly (ADP-ribose) synthetase [6] and, at high concentrations, can act as a free radical scavenger [17]. Pre-treatment with nicotinamide prevents the decrease in proinsulin synthesis in islets from rats treated with alloxan or streptozotocin [18]. It also inhibits the activated macrophage killing of Beta cells in vitro [19], and the expression of Class 2 MHC on Beta cells caused by the cytokines, tumour necrosis factor (TNF) and δ-interferon [20]. These are all processes thought to be part of the immune-mediated destruction of Beta cells found in the human disease.

Although nicotinamide has been postulated as a cocarcinogen in animals [21], there was no evidence of endocrine tumours after 450 days of high-dose nicotinamide treatment in BB rats [8]. We are unaware of any toxicity reported from nicotinamide in the human other than transient liver enzyme changes and jaundice when a bottle of tablets was swallowed in a suicide gesture. In 35 newly-diagnosed children with Type 1 diabetes given nicotinamide on a double-blind basis, no treated child had even a transient elevation of liver enzymes [11].

The level of cut-off for FPIR used in this study (< 67 mU/l) was arbitrary, as normal FPIR is influenced by age and puberty [22]. Similarly, we do not know whether a given elevated level of ICA has equivalent prognostic significance within the age range of the subjects studied. However, the mean ages of the control subjects (8.9 years) and of the treated subjects (6.3 years) were similar, and the same FPIR level was used for both the control and the treated groups.

A recent report [23] described two children (ages 8 and 11 years) and one adult (age 28 years) who were also given nicotinamide in the pre-diabetes period and who progressed to insulin-dependence. The adult had already gone over two and a half years after the first-phase insulin level was below 30 μU/ml, and had received three courses of prednisone prior to starting the nicotinamide. The eight-year-old went approximately 2 years after having a first-phase insulin below 30 μU/ml prior to needing to start insulin (after approximately 21 months of nicotinamide therapy). These data, in addition to the data for the subject in our study (insulin-dependent after 24 months of nicotinamide treatment) suggest that when treatment with nicotinamide is started late in the diabetogenic process (FPIR < 30 μU/ml), it is effective only in delaying insulin-dependence rather than in preventing it.

The results of this trial demonstrate that the onset of Type 1 diabetes in humans has been delayed by the use of nicotinamide. The better response found in those with higher initial insulin release suggests that nicotinamide will be more effective given early in the course of Beta-cell destruction, and will be ineffective late in the course. How long the delay in diabetes onset will persist, and how long the nicotinamide needs to be given, are questions requiring answers. Clearly, a multicentre double-blind study of the effects of nicotinamide on the prevention of Type 1 diabetes is now indicated.

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