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Rapid communications

Nicotinamide and insulin secretion in normal subjects

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Summary. Nicotinamide has been given both before and after clinical onset of Type 1 (insulin-dependent) diabetes mellitus in an attempt to prolong beta-cell survival. Nicotinic acid, structurally similar to nicotinamide, induces insulin resistance and increases insulin secretion in healthy individuals. It is not known if nicotinamide has similar effects. Since insulin secretion, as measured by the acute insulin response to intravenous glucose, is used to predict diabetes and to monitor therapy, the effects of nicotinamide must be established before trials in individuals at high risk of progression to Type 1 diabetes can be interpreted. Intravenous tolerance tests were performed according to the ICARUS standard protocol in 10 healthy, adult subjects (age 32 ± 5.7 years) before and after 14 days of treatment with nicotinamide 25 mg · kg^{-1} · day^{-1}. The acute insulin response after nicotinamide did not differ from the control study, whether measured as the incremental 0–10 min insulin area (278 ± 142 vs 298 ± 130 mU · l^{-1} · 10 min^{-1}) or as the 1 ± 3 min insulin level (78 ± 39 vs 81 ± 44 mU/l). The late insulin response was equally unaffected, as were basal insulin (5.2 ± 1.6 vs 5.6 ± 2.1 mU/l) and glucose (5.0 ± 0.4 vs 4.9 ± 0.2 mmol/l) levels and glucose disposal rates (1.98 ± 0.88 vs 2.04 ± 0.68 %/min). Nicotinamide does not affect insulin secretion and glucose kinetics in normal subjects, confirming its suitability for trials designed to delay or prevent the onset of Type 1 diabetes.

Key words: Nicotinamide, niacinamide, insulin secretion, intravenous glucose tolerance test, prevention.

Nicotinamide (vitamin B_3) is of potential value in delaying the onset of Type 1 (insulin-dependent) diabetes mellitus. It is effective in the non-obese-diabetic mouse [1] and has shown promising results in man [2]. This study forms part of the preparation for a multinational controlled trial in high risk family members of patients with Type 1 diabetes which will begin shortly.

Nicotinamide is the amide of nicotinic acid and the two are structurally similar. The two compounds can potentially be interconverted in vivo, and at pharmacological concentrations nicotinamide may be deamidated to nicotinic acid in the course of detoxification [3]. Nicotinic acid induces insulin resistance and is used for this purpose experimentally. In normal individuals glucose homeostasis is maintained by increased insulin secretion [4], but nicotinic acid may precipitate diabetes or impaired glucose tolerance in animals with partial beta-cell destruction [5]. The humans who will participate in intervention studies are analogous to such animal models, since the presence of immune markers is presumed to reflect ongoing autoimmune beta-cell destruction. Insulin responses to the intravenous glucose tolerance test (IVGTT) are reduced in the latter stages of the pre-diabetic prodrome [6] and abnormalities of glucose tolerance also appear [7]. Therapy which induces insulin resistance might therefore accelerate rather than delay the onset of diabetes.

We attempted to establish whether nicotinamide, at the dose planned for the intervention trial, affects insulin secretion or glucose handling in response to the IVGTT in healthy individuals.

Subjects and methods

Ten healthy non-obese adult subjects, age 32 ± 5.7 years, body mass index 21.7 ± 1.6 kg · m^{-2}, were studied. Each had an IVGTT before and after 14 days of treatment with soluble nicotinamide 25 mg · kg^{-1} · day^{-1} in two divided doses. The preparation, kindly donated by FERROSAN (Copenhagen, Denmark), contained approximately 0.1 % nicotinic acid on fluid phase liquid chromatography. Nicotinamide was dissolved in water before ingestion and the last dose was given on the morning of the second test. The IVGTT was performed according to the ICARUS protocol [8]. Subjects were asked to have at least 150 g carbohydrate in their diet for 3 days prior to the test and to fast overnight. The tests were performed between 07.30 and 09.30 hours. Glucose (0.5 g/kg) was given as a 25 % solution over

3 min into an antecubital fossa vein. Two basal samples were taken with further samples 1, 3, 5, 7, 10, 15, 20, 30, 45 and 60 min after the end of the infusion. Plasma was separated immediately and stored at −20 °C until assayed.

Assays

Immunoreactive insulin was determined using a double-antibody radioimmunoassay with guinea-pig anti-porcine-insulin as first antibody (Immunodiagnostic Systems Ltd, Washington, Northumberland, UK) and sheep anti-guinea pig Fc (International Laboratory Services, London, UK) as the second antibody. ^{125}I-labelled human insulin (specific activity 2000 Ci/mmol; Amersham International PLC, Amersham, Bucks., UK) was used as tracer with human insulin standards (Novo Biolabs, Bagsvaerd, Denmark). Plasma glucose was assayed by a glucose oxidase method using a YSI model 23AM glucose analyser (Yellow Springs Instrument Co., Yellow Springs, Ohio, USA).

Statistical analysis

The acute (first phase) and late (second phase) insulin responses to intravenous glucose were calculated as the 0–10 min and 10–60 min areas under the curve using trapezoidal integration. The glucose disposal rate (K_g) was expressed as the slope of the semi-logarithmic decline of blood glucose over the 10 to 30 min following glucose infusion. Comparisons were made using the one-sample *t*-test on log transformed data. Results are expressed as mean ± SD.

Results

Figure 1 (upper panel) shows the mean insulin levels before and after treatment with nicotinamide. The mean acute insulin response, measured as the 0–10 min insulin area, was 298 ± 130 mU·l^{-1}·10 min^{-1} prior to treatment and did not change after nicotinamide (278 ± 142 mU·l^{-1}·10 min^{-1}) (Fig. 1, lower panel). The sum of the 1- and 3-min insulin levels was 81 ± 39 mU/l before and 78 ± 39 mU/l after treatment. The late insulin response was also unchanged. Basal insulin (control 5.6 ± 2.1 vs 5.2 ± 2.1 mU/l after treatment) and glucose (4.9 ± 0.2 vs 5.0 ± 0.4 mmol/l) levels and glucose disposal rates (2.04 ± 0.68 vs 1.98 ± 0.88 %/min) were also unaffected.

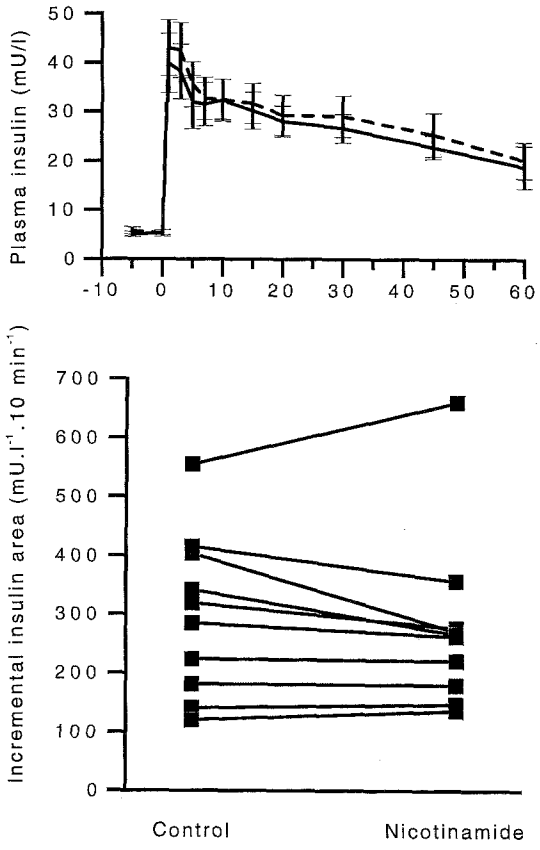

Fig. 1. Upper panel: insulin levels (mean ± SEM) in intravenous glucose tolerance tests performed before (-----) and after (——) 14 days of treatment with nicotinamide. Lower panel: individual acute insulin responses (measured as the incremental 0–10 min area under the insulin curve) before and after 14 days of treatment with nicotinamide

Discussion

The ratio of risk to benefit requires careful consideration when planning studies aimed at prevention of Type 1 diabetes [9]. Nicotinamide appears sufficiently safe to be tested in individuals with only a moderate risk of diabetes (35 % over 5 years) [10], and has been taken as a vitamin supplement or, at high doses, as potential therapy for a variety of conditions over many years.

Pilot studies in newly-diagnosed diabetic patients or islet cell antibody positive non-diabetic subjects have used pharmacological doses, approximately 100 times the recommended daily intake. The concern that gave rise to the present study was that most, if not all, of those exposed to high-dose nicotinamide will have subclinical beta-cell dysfunction, which might potentially be aggravated by therapy which affects insulin secretion or action. Its structural similarity with nicotinic acid suggests that nicotinamide might share its unwanted metabolic effects; indeed the two compounds might be interconverted in vivo, particularly at high doses, both as part of the detoxification process and as a result of hydrolysis of nicotinamide by gastric acid [3]. Administration of nicotinic acid raises circulating non-esterified fatty acid levels and induces insulin resistance [5]. Normal beta-cell reserve maintains normal glucose homeostasis at the cost of increased insulin secretion, both in man and in animal models [4, 5]. Individuals unable to compensate by increased insulin secretion would be expected to develop glucose intolerance. Changes in fasting glucose became apparent in high-dose streptozotocin treated baboons within a few days of starting nicotinic acid. A lower dose of streptozotocin produced partial beta-cell destruction and the animals showed compensatory increases in acute insulin responses with nicotinic acid but there was a significant increase in HbA_{1c} levels over the 20 days of treatment [5].

Assessment of stimulated insulin secretion, in conjunction with glucose disposal provides an indirect measure of insulin resistance, which can be supplemented by consideration of basal glucose and insulin levels. We chose to use the IVGTT for this study, even though this may be less

sensitive to minor differences in insulin sensitivity than the hyperinsulinaemic euglycaemic clamp. This was because the IVGTT allows us to examine insulin secretion and glucose handling at insulin levels encountered in everyday life, and will be used in the trial both as an entry criterion and possibly as an outcome measure.

The formulation and presentation of nicotinamide might also be important. Levels of purity of vitamin preparations are less stringently regulated than those of other pharmaceutical preparations, and commercially available nicotinamide, as used in this study, contains nicotinic acid among a number of other impurities. These can safely be disregarded at replacement doses but are potentially relevant at pharmacological levels. The intervention trial will use a highly purified sustained release form of nicotinamide, but the soluble form was used in this study on the basis that metabolic effects would more readily become apparent in response to this challenge.

We found no change in insulin secretion after 14 days of treatment with high doses of nicotinamide. Basal insulin levels were unchanged, and first and second phase insulin responses in the IVGTT were similar before and after treatment. The intra-individual coefficient of variation was well within the range normally encountered in the test. Fasting levels of insulin and plasma glucose were equivalent before and after treatment, as were glucose disposal rates.

In conclusion, short-term administration of high doses of nicotinamide does not affect basal or stimulated insulin secretion or glucose kinetics in healthy subjects and is therefore unlikely to have a significant effect on insulin sensitivity. This preliminary study cannot exclude all possible metabolic effects of nicotinamide, but it does provide reasonable reassurance that these are unlikely to be of clinical importance. It also suggests that no major conversion of nicotinamide to nicotinic acid occurs, even at high doses. It remains possible that nicotinamide could produce minor changes that would not become apparent in those with normal beta-cell function but which could prove relevant in "pre-diabetic" individuals, particularly over the longer term. Careful surveillance of metabolic variables should therefore form part of the interim analysis in a placebo-controlled trial. Our findings, however, endorse the suitability of nicotinamide for trials designed to delay or prevent the onset of Type 1 diabetes.

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References

1. Yamada K, Nonaka K, Hanafusa T, Miyazaky FM, Toyoshima H, Tauri S (1982) Preventive and therapeutic effects of large dose nicotinamide injections on diabetes associated with insulitis. Diabetes 31: 749–753
2. Elliott RB, Chase PH (1991) Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. Diabetologia 34: 362–365
3. Lee YC, Chandler JLR, Gholson RK (1971) Quantitative studies on the excretory metabolites of nicotinic acid and nicotinamide in normal, hypophysectomized, and germ-free rats. In: Gey KF, Carlson LA (eds) Metabolic effects of nicotinic acid and its derivatives. Hans Huber, Berne, pp 133–147
4. Kahn SE, Beard JC, Schwartz MW et al. (1989) Increased beta-cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced resistance. Diabetes 38: 562–568
5. McCulloch D, Kahn SE, Schwatz MW, Koerker DJ, Palmer JP (1991) Effect on nicotinic acid-induced insulin resistance on pancreatic B cell in normal and streptozocin-treated baboons. J Clin Invest 87: 1395–1401
6. Vardi P, Crisa L, Jackson RA et al. (1991) Predictive value of intravenous glucose tolerance test insulin secretion less than or greater than first percentile in islet cell antibody positive relatives of type 1 (insulin-dependent) diabetic patients. Diabetologia 34: 93–102
7. Tarn AC, Smith CP, Spencer KM, Bottazzo GF, Gale EAM (1987) Type 1 (insulin-dependent) diabetes: a disease of slow clinical onset? BMJ 294: 342–345
8. Bingley PJ, Colman PG, Eisenbarth GS et al. (1992) Standardization of the intravenous glucose tolerance test for use in the prediction of insulin-dependent diabetes. Diabetes Care 15: 1313–1316
9. Bingley PJ, Bonifacio E, Gale EAM (1993) Can we really predict IDDM? Diabetes 42: 213–220
10. Chase P, Dupre J, Mahon J et al. (1992) Nicotinamide and prevention of diabetes. Lancet 339: 1051–1052

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