Review

Safety of high-dose nicotinamide: a review

M. Knip[1]**, I. F. Douek**[2]**, W. P. T. Moore**[2]**, H. A. Gillmor**[2]**, A. E. M. McLean**[3]**, P. J. Bingley**[2]**, E. A. M. Gale**[2]**, for the ENDIT Group***

[1] Department of Paediatrics, Medical School, University of Tampere, Finland
[2] Diabetes and Metabolism, Division of Medicine, University of Bristol, UK
[3] Department of Clinical Pharmacology, University College London Medical School, UK

Abstract

Nicotinamide, the amide derivative of nicotinic acid, has over the past forty years been given at high doses for a variety of therapeutic applications. It is currently in trial as a potential means of preventing the onset of Type I (insulin-dependent) diabetes mellitus in high-risk, first-degree relatives. Nicotinamide is for regulatory purposes classed as a food additive rather than a drug and has not therefore required the formal safety evaluation normally expected of a new therapy. Because the safety of treatment with megadoses of vitamins cannot be assumed, a full literature review has been undertaken. The therapeutic index of nicotinamide is wide but at very high doses reversible hepatotoxicity has been reported in animals and humans. Minor abnormalities of liver enzymes can infrequently occur at the doses used for diabetes prevention. There is no evidence of teratogenicity from animal studies and nicotinamide is not in itself onco- genic; at very high doses it does however potentiate islet tumour formation in rats treated with streptozo- tocin or alloxan. There is no evidence of oncogenicity in man. Growth inhibition can occur in rats but growth in children is unaffected. Studies of its effects on glucose kinetics and insulin sensitivity are incon- sistent but minor degrees of insulin resistance have been reported. The drug is well tolerated, especially in recent studies which have used relatively pure preparations of the vitamin. Experience to date therefore suggests that the ratio of risk to benefit of long-term nicotinamide treatment would be highly favourable, should the drug prove efficacious in dia- betes prevention. High-dose nicotinamide should still, however, be considered as a drug with toxic po- tential at adult doses in excess of 3 gm/day and unsu- pervised use should be discouraged. [Diabetologia (2000) 43: 1337–1345]

Keywords Type I diabetes, nicotinamide, prevention.

Introduction

High-dose nicotinamide therapy has protective effects on beta-cell survival and function in response to a range of toxic and immune stimuli in animal and in vitro models. Potential therapeutic benefits might be related to its actions as a free radical scavenger, to its availability as a component of the coenzyme nicotinamide adenine dinucleotide (NAD), or to par- tial inhibition of the nuclear DNA repair enzyme poly(ADP)-ribose polymerase (PARP) which also modulates major histocompatibility complex (MHC) class II expression and apoptosis [1–3]. Nicotinamide also inhibits ADP-ribosyl transferring enzymes mod- ulating immune cell function and survival [3]. It has been tested in a number of human studies as a possi- ble means of preserving beta-cell survival after diag- nosis of Type I (insulin-dependent) diabetes mellitus and is currently undergoing large scale evaluation in controlled trials in first-degree relatives at high-risk

Corresponding author: Prof. E. A. M. Gale, Department of Di- abetes and Metabolism, Medical School Unit, Southmead Hospital, University of Bristol, BS10 5NB, UK
Abbreviations: PARP, Poly(ADP)-ribose polymerase; 2pyr, *N*- methyl-2-pyridone-5-carboxylic acid amide; ICA, islet cell an- tibody; ENDIT, European Nicotinamide Diabetes Interven- tion Trial.

* see Acknowledgements

of progression to Type I diabetes. Although high-dose nicotinamide has a good safety record in human studies, massive doses could in some situations have teratogenic, oncogenic and growth retarding effects in animals. These data are reviewed and the potential risks of high-dose nicotinamide in the attempted prevention of Type I diabetes are outlined.

Niacin, first isolated from rice bran in 1911 and more commonly known as Vitamin B3, is a water soluble vitamin with a recommended daily allowance of $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. It was later recognised to have two distinct but chemically related components, nicotinamide and nicotinic acid. Its deficiency causes pellagra in man. Nicotinamide, first isolated from horse erythrocytes in 1935 [4], is the amide derivative of nicotinic acid. It is a bitter tasting, white, odourless, crystalline powder. The structure consists of a pyridine ring with an amide group in position three. Nicotinamide is a component of NAD, a coenzyme involved in many cellular oxidation-reduction reactions. Despite similarities in chemical structure, nicotinamide and nicotinic acid have very different actions and clinical uses.

Nicotinamide or nicotinic acid or both have been used for many years at high doses in the attempted treatment of a variety of disorders [5–12]. Recent attention has focused on the possibility that nicotinamide might have useful actions in preserving beta-cell function before or after diagnosis of Type I diabetes [13–20]. Its safety in otherwise healthy children and adults is clearly of major importance. The question of dosage needs particular emphasis. The recommended daily intake is about 20 mg (0.2 mmols) a day for an adult or around $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. In contrast, the dose used in diabetic and prediabetic patients has ranged from $25\text{–}50 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (1.75–3.5 g/day). Such pharmacological doses clearly require toxicological scrutiny.

Knowledge of the potential toxicity of nicotinamide is based on a wide range of animal studies and relatively extensive use of high-dose nicotinamide treatment in humans. It is, however, classed as a food additive rather than a pharmaceutical agent and has never undergone the full formal safety evaluation routinely expected of new therapeutic agents. The literature on nicotinamide, although extensive, spans more than 50 years. This has complicated evaluation because, for example, early studies often confuse the side effects of nicotinic acid and nicotinamide, and mixtures have occasionally been used. Further, the purity of the nicotinamide preparations can vary considerably and some preparations include small amounts of nicotinic acid.

Pharmacokinetics of nicotinamide

The pharmacokinetics of nicotinamide are dependent on dose, species, sex and route of treatment [21–25] and metabolic pathways differ according to the species studied [22, 23, 26]. Nicotinamide is readily absorbed parenterally and from all parts of the gastrointestinal tract [4] and peak concentrations are achieved in humans within about 1 hour of oral ingestion of standard preparations [27]. Nicotinamide disappears rapidly from the circulation and is distributed in all tissues. It has a high hepatic extraction ratio and plasma clearance can be reduced in patients with hepatic insufficiency.

Nicotinamide can be oxidised to nicotinamide-N-oxide, methylated to N-methyl-nicotinamide or hydroxylated to 6-hydroxynicotinamide (Fig. 1). There is no evidence that nicotinamide is metabolised to nicotinic acid in rodents or humans [27, 28]. Hepatic methylation using l-methionine as a methyl donor is important in the detoxification of nicotinamide [23]. The product of this reaction, N-methyl-nicotinamide, is excreted by the kidneys whereas nicotinamide is reabsorbed by the renal tubules [29]. For this reason only small amounts of the unchanged vitamin appear in the urine even at pharmacological doses of nicotinamide. N-methyl nicotinamide is oxidised in the liver, a process that is saturated at high circulating concentrations, and the end products are N-methyl-2-pyridone-5-carboxylic acid amide (2 pyr) and N-methyl-4-pyridone-3-carboxylic acid amide (4 pyr). The ratio of the two metabolites differs with species and sex. In humans 2 pyr is formed exclusively [28]. Nicotinamide oxidation to nicotinamide-N-oxide can also be an important pathway at very high doses in humans and other species [23, 30].

Single dose toxicity

The LD_{50} s. c. of nicotinamide in rats is 1.68 g/kg [31]. The LD_{50} in mice is estimated as 4.5 g/kg when given orally and 2.5 g/kg when given intravenously [32]. The therapeutic index of the preparation is correspondingly wide.

Repeated dose toxicity

Potential toxic effects of nicotinamide in animal and human studies are summarised in Table 1.

Liver toxicity

Older clinical studies using nicotinic acid or impure preparations of nicotinamide reported relatively frequent liver enzyme abnormalities [6, 33–35] although
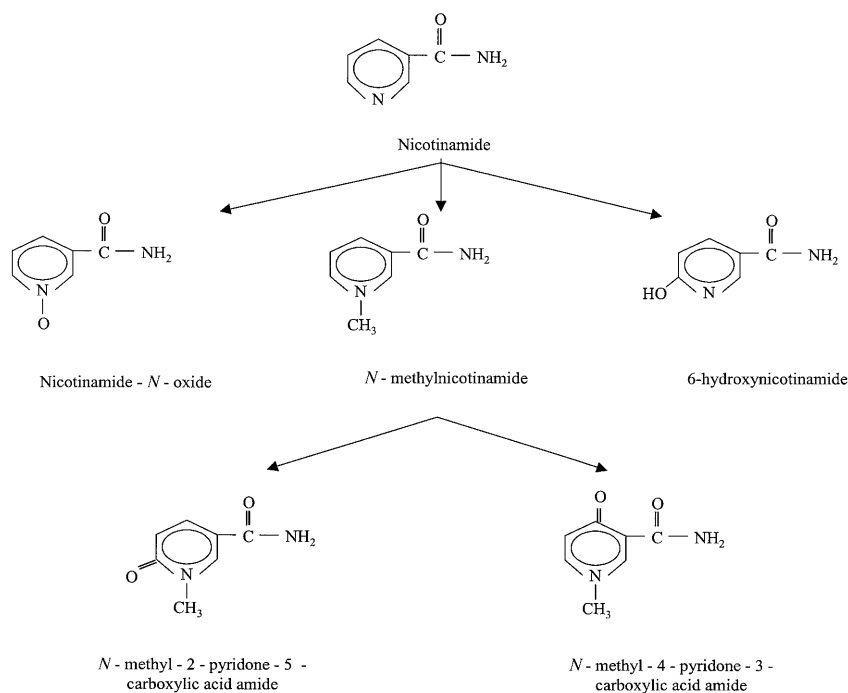
Fig. 1. The pharmacokinetics of nicotinamide [23]

more recent studies using a purified form of nicotinamide have not detected any noteworthy adverse effects on liver enzymes [13, 15, 17, 20, 36]. This experience is described in more detail below.

Nicotinamide at a dose of $500\ \mathrm{mg \cdot kg^{-1} \cdot 12\ h^{-1}}$ given i.p in rats resulted in liver cell enlargement and glycogen deposition with an increase of total hepatic lipids by almost 50 %. This effect seemed to be greater in females and was less pronounced when nicotinamide was given orally. Supplementation of the diet with 0.5 % nicotinamide in rats increased liver fatty acids from 4.3 to 15.8 %. The addition of 2 % nicotinic acid to the diet led to a similar rise from 4.2 to 11.8 %. The authors did not, however, examine the livers histologically [25]. These findings have not been confirmed in other studies [37, 38] which found no increase in liver content of fatty acids nor any histological signs of fatty liver degeneration. There is also some evidence that nicotinic acid can protect the liver from the toxic influence of other agents and intraperitoneal injection of the vitamin for 2–3 days at a dose of approximately $300\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ protected rats against lethal doses of carbon tetrachloride [39].

Table 1. Potential toxic effects of nicotinamide in experimental and human studies

Toxicity	Animal data	Human data
Liver toxicity	0.5 % supplementation of diet: increase in liver fatty acids [25], not confirmed by subsequent studies [37, 38]	Jaundice with a frequency of 1:2000 [40]
Teratogenicity	Chick embryos 2.5 mg/egg: coteratogen with acetazolamide [45] 19 mg/egg: inhibition of teratogenic effect of insulin and sulphonamide [42, 44]	No evidence [40]
Oncogenicity	Rodents 350 mg/kg: no detectable carcinogenic action [46] 1 % supplementation of drinking water lifelong: no apparent carcinogenic action [47] 305–500 mg/kg: coteratogen for islet cell tumours together with streptozotocin and alloxan [46, 49–51]	No evidence [5–20, 33, 35, 52–57]
Growth-retarding	1 % supplementation of diet: growth inhibition in rats [25] but no effect in rabbits or guinea-pigs [26]	No retardation of growth [19, 20]
Insulin response	No evidence	25 mg/kg, 1.2 g/m²: no effect in normal subjects [61, 62] 25 mg/kg, 1 g/day: improved stimulated C-peptide secretion in newly diagnosed Type I diabetic patients [13, 36] 1.2 g/m²: decreased first-phase insulin response in prediabetic subjects [20]

Assessment of liver toxicity in humans should, as noted, be interpreted with caution because the majority of studies are old and mixtures of nicotinamide and nicotinic acid were often used. In a study on 41 children with attention deficit disorders treated daily for 3 months with a megavitamin regimen comprising 3 g of nicotinamide and ascorbic acid, 1.2 g of calcium pantothenate and 0.6 g of pyridoxine during the last 2 weeks, 17 (42 %) subjects showed an increase of serum transaminase concentrations, which in some cases took 4 to 6 weeks to remit [33]. Serum bilirubin values also tended to increase but no child had values above the upper limit of the reference range. It was suggested that nicotinamide was responsible for the liver enzyme abnormalities but as the vitamins were not tested separately this could not be concluded with any certainty. A 35-year-old schizophrenic man developed hepatic toxicity after a daily dose of 9 g nicotinamide [34]. The patient presented with nausea and vomiting and had increased serum transaminase and bilirubin concentrations. A liver biopsy showed increased portal fibrosis and cholestasis. After discontinuation of nicotinamide the symptoms disappeared rapidly and all liver function tests returned to normal values in 3 weeks. A nicotinamide challenge was later done in this patient resulting in reappearance of the symptoms and increased transaminase concentrations in less than 2 weeks. This report illustrates that very large doses of nicotinamide can be hepatotoxic in susceptible people.

Hoffer [40] has stated that the incidence of liver damage as indicated by jaundice caused by nicotinamide or nicotinic acid is very low. In a survey by the Committee on Therapy of the American Schizophrenia Foundation three cases of jaundice were reported out of a total number of 6000 patients treated with megadoses of nicotinamide or nicotinic acid. In one of these patients, treated with nicotinic acid 6 g/day, jaundice resolved when simultaneous phenothiazine treatment was discontinued and in another patient jaundice cleared although treatment with nicotinic acid was resumed. Altschul was reported as finding only four cases of jaundice in a complete literature review [40], and two of these patients were being treated with slow release nicotinic acid. In the Coronary Drug Project minor increases of serum glutamate oxaloacetate transferase and serum alkaline phosphatase were observed in 1119 subjects receiving nicotinic acid 3 g daily for 5 years [35]. Based on his experience over 6 years of treatment with nicotinic acid, Parsons [6] suggested that abnormal liver function tests do not indicate hepatocellular damage but represent changes in liver enzymes, which are rapidly reversible when the drug is discontinued.

One human study has reported that high-dose nicotinamide was able to protect against short-term hepatotoxic effects produced by drinking large amounts of ethanol in white wine [41]. The oxidation of ethanol leads to an increase in the NADH:NAD ratio which secondarily decreases the activity of key enzymes on ATP-producing pathways and so decreases the production of albumin and fibrinogen by the liver. When nicotinamide is given with ethanol and a standard meal it counteracts this effect and so restores the meal-induced increase in albumin and fibrinogen.

Other toxic effects

No hyperuricaemic effect has been reported during nicotinamide treatment. In contrast nicotinic acid increases uric acid concentrations in some subjects but attacks of gout are extremely rare [40]. Other toxic effects associated with the use of high doses of nicotinic acid are bullous lesions of the skin, toxic amblyopia and hypotensive reactions [32]. No such effects have been reported in connection with megadoses of nicotinamide.

Reproduction

The teratogenic effects of nicotinamide have been studied in chick embryos by injection of the vitamin into the yolk sack of the egg in doses of 2–19 mg/egg. These experiments provide no evidence that nicotinamide is teratogenic by itself [42–44], although it did increase the frequency of acetazolamide-induced malformations in the anterior parts of the embryo from 37.6 to 57.1 % at a dose of 2.5 mg/egg [45]. In contrast, nicotinamide at a dose of 19 mg/egg decreased the rate of insulin-induced malformations from 41.7 to 5.9 % [42] and was also shown to decrease the rate of sulphonamide-induced malformations [44]. Hoffer reports that Altschul gave nicotinic acid to rabbits before mating and through gestation without harmful effect and he himself gave nicotinic acid to pregnant patients without untoward consequences. He even suggests large doses can prevent some forms of embryonal damage due to a deficiency of NAD [40].

Oncogenic potential

Because nicotinamide potentially promotes survival of cells with DNA damage, possible oncogenicity is an issue of concern, particularly when long–term use of the drug is considered in children and adolescents. Nicotinamide does not seem to have any oncogenic effect when given alone. Two intraperitoneal injections of nicotinamide at a dose of $350 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{injection}^{-1}$ when given alone did not result in any detectable carcinogenic action in adult rats [46]. In another study giving 1 % nicotinamide in drinking water

to Swiss mice from 6 weeks of age continuously and lifelong had no oncogenic effect [47]. Nicotinamide can however potentiate the ability of streptozotozin or alloxan to induce pancreatic islet cell tumours in rodents [46, 48–51]. The dose of nicotinamide used in these experiments was high, ranging from 305 to 500 mg/kg. There has been no suggestion of oncogenic effects in humans despite high-dose treatment of more than 2000 people in studies dating back over many years [5–20, 33, 35, 52–57]. The quality and completeness of follow-up in these reports is however variable. It is therefore most important that future studies of nicotinamide in prediabetes where DNA damage has already occurred include careful long-term follow-up for evidence of oncogenicity.

Effects on growth

Growth inhibition in rats was first shown in 1942, after inclusion of 1% nicotinamide in the diet. This effect, which was not seen with nicotinic acid, was completely reversed by inclusion of methionine in the diet [25]. No effect on growth was found in young rabbits and guinea-pigs [26]. Inhibition of growth in rats might be due to increased synthesis of N-methyl nicotinamide, resulting in a methionine and hence choline deficiency; the effects of paracetamol upon growth in rodents have a similar basis [58]. If so the species difference is easily explained, as methylation to N-methyl nicotinamide is not the major route of metabolism in the rabbit or guinea-pig. The unpleasant taste of nicotinamide in solution might explain why food intake was reduced by almost half in nicotinamide-treated animals in one study [25].

A low methionine diet does not affect hepatic methylation in humans [59] and nicotinamide has not been shown to affect growth in children. When height and weight were monitored in 173 children under the age of 12 who were positive for islet cell antibodies (ICA) and were treated with nicotinamide (1 g daily) and for whom two or more readings for height and weight were available, a regression across time showed no change in standard deviation units of height, suggesting that linear growth was not affected [19]. The Deutsche Nicotinamide Intervention Study (DENIS) found no retardation of body growth in 25 ICA-positive children aged 3–12 years and treated with nicotinamide for a median of 2.1 years compared with 30 ICA-positive children of similar age who were treated with placebo [20]. The interim analysis of the safety committee for the ongoing European Nicotinamide Diabetes Intervention Trial (ENDIT), which reviewed data on 734 patient-years of follow-up for 331 ICA-positive family members under the age of 20 taking nicotinamide $1.2 \text{ g} \cdot \text{m}^{-2} \cdot \text{day}^{-1}$ or placebo has reported no concerns regarding growth (ENDIT review committee, personal communication).

Effects on glucose kinetics and insulin secretion

Nicotinamide has no effect in vitro using human islets [60]. Glucose kinetics or basal or stimulated insulin concentrations are unaffected in healthy subjects [61, 62]. In contrast nicotinic acid can induce insulin resistance and glucose intolerance [40]. In patients with recently diagnosed diabetes a meta-analysis of 10 randomised controlled trials found that basal C-peptide concentrations were higher in patients receiving nicotinamide than in those receiving placebo 12 months from diagnosis [63]. Published studies of nicotinamide treatment in people at increased risk of developing diabetes have produced varying results. In one small study insulin sensitivity decreased after two weeks of nicotinamide, although basal and stimulated insulin secretion were unchanged [64], whereas DENIS found a decreased first-phase insulin response in nicotinamide-treated people at 2 years [20].

Tolerability

Nicotinamide is unpalatable when taken in solution and is usually given in capsules or in tablet form. At high doses older studies have reported an overall frequency of side effects of less than 5% [40, 65]. Potential side effects from the older literature are listed in Table 2. In contrast to nicotinic acid, nicotinamide is not a vasodilator and rarely produces cutaneous flushing [66]. Other mucocutaneous adverse effects occurred in less than 1% of subjects. Heartburn is a rare side effect of nicotinamide, and other gastrointestinal symptoms include vomiting, flatulence, soft stools and diarrhoea. Vomiting is rarer with nicotinamide than with nicotinic acid but the incidence of nausea and vomiting can increase during viral infections. Mild headache and dizziness have been reported after giving nicotinamide parenterally [67]. After

Table 2. Side effects of nicotinamide and available data on their frequency when using high doses of the vitamin [40, 65, 69]

Side-effect	Reported frequency
Flushing	≤ 1.5%
Facial erythema	≤ 0.5%
Hives	≤ 0.4%
Sore mouth	≤ 0.4%
Dull headache	≤ 0.5%
Heartburn	≤ 1.6%
Nausea (with radiotherapy)	17–65%
Nausea (without radiotherapy)	≤ 1.5%
Other gastrointestinal symptoms	≤ 0.8%
Inability to focus the eyes	≤ 0.4%
Dry hair	≤ 0.4%
Fatigue	≤ 0.4%

Table 3. Experience with use of megadoses of nicotinamide in different diseases

Year	Indication	Number of people		Dosage	Time Exposed	Comments	Reference
		nicotinamide	placebo				
1987	Newly diagnosed Type I diabetes	7	9	3 g/day	6 months	Remission rate assessed	14
1989	Newly diagnosed Type I diabetes	10	10	1 g/day	45 days		13
1989	Newly diagnosed Type I diabetes	23		200 mg/day	12 months	Open trial	53
1989	Type I diabetes with residual insulin secretion	11	12	3 g/day	9 months	Average 2 years post diagnosis	15
1990	Newly diagnosed Type I diabetes	18	17	100 mg/year old (max 1.5 g/day)	12 months		17
1992	Newly diagnosed Type I diabetes	29	20	40 mg/kg	6 months		16
1995	Newly diagnosed Type I diabetes	28	28	25 mg/kg	12 months		36
1999	Newly diagnosed Type I diabetes	38 36		25 mg/kg 50 mg/kg	12 months	comparison of 25 mg/kg with 50 mg/kg of nicotinamide	70
1991	At high risk of Type I diabetes	14	8	150–300 mg/year old (max 3 g/day)	17 months mean		18
1996	At high risk of Type I diabetes/general population	173	48335c 13463r	1 g/day	30 months	Schoolchildren. Placebo group includes controls (c) + refusals (r)	19
1998	At high risk of Type I diabetes	25	30	1.2 g/m^2	2.1 years median		20
2003	ENDIT	276	276	1.2 g/m^2	Up to 5 years		
1983	Granuloma annulare	1		1.5 g/day	6 months		12
1986	Polymorphous light eruption	42		3 g/day	2 weeks	Open trial	56
1988	Necrobiosis lipoidica	13		1.5 g/day	> 1 month	Open trial	9
1998	Pemphigoid	8		2.5–3 g/day	6 months	Added to minocycline	57
1952–1969	Schizophrenia	982		1.5–6 g/dy	?	Nicotinamide or nicotinic acid given	40
1968	Schizophrenia	262		3 g/day	3–36 months mean 9 months	Personal communication	40
1970	Schizophrenia	17 16 T	24	1 g/23 kg	6 months	16 given tranquilisers (T) with nicotinamide	8

max = maximum

treatment for 2 weeks, side effects of flushing, skin sensations and gastrointestinal symptoms usually resolve [67]. The majority of reported side effects have been reversible after discontinuation of the drug [68]. These findings should be interpreted with some caution because, as indicated earlier, few studies have used pure preparations of nicotinamide.

Experience with use of megadoses of nicotinamide in different diseases

The following studies are summarised in Table 3.

Schizophrenia

Nicotinamide and nicotinic acid were used as adjunctive treatments in a number of psychiatric conditions in studies dating back to the late 1940 s. Hoffer was a strong advocate of its use in the management of schizophrenia and collected data on over 1000 patients who were given nicotinamide or nicotinic acid (1.5–6 g/day) for 3 months to 5 years duration [40]. The American Schizophrenia Foundation also collected information on the use of megavitamin therapy (including nicotinamide) for more than 2 years on 6000 patients and reported an overall incidence of

side effects of less than 5 per cent, with none considered major [40].

Skin conditions

Beneficial effects have been described in over 60 case reports where nicotinamide has also been used in the treatment of polymorphous light eruptions, necrobiosis lipoidica and pemphigoid [9, 12, 56, 57]. Doses ranged from 1.5–3 g/day given for durations of 2 weeks to 6 months with few adverse effects.

Radiotherapy

More recently megadoses of nicotinamide have been used in clinical studies in combination with accelerated radiotherapy and carbogen (ARCON) to radiosensitize inoperable tumours. Its benefit in this situation is apparently due to increased blood flow through the tumour region. Nicotinamide (80 mg/kg, maximum 6 g) is given 1 hour before radiotherapy and continued for the duration of each course of radiotherapy. Preliminary reports from a research workshop using ARCON showed impressive improvements in local control of inoperable head and neck tumours and T3 bladder tumours compared with historical data [69]. Patients undergoing accelerated radiotherapy for head and neck tumours receive nicotinamide at very high doses of $80 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (6 g maximum) and frequently report nausea [69]. This usually occurs within 1 week of starting treatment and is difficult to control with anti-emetics. In patients with unacceptable nausea and vomiting a 25 % dosage reduction made symptoms more manageable and symptoms stopped on cessation of therapy.

Type I diabetes

Adjunctive nicotinamide treatment has been reported in 200 people with newly diagnosed Type I diabetes or in longer duration patients with residual insulin secretion. Doses have ranged from 200 mg/day to 50 mg/kg (equivalent 3.5 g/day) for 12 months [13–17, 36, 53, 70]. Only one minor clinical and no biochemical adverse events were noted in these studies.

Nicotinamide has also been used in 200 people at high risk of developing Type I diabetes at doses of 1 g/day to 3 g/day for 4 months to 4 years [18–20]. In addition ENDIT is currently conducting a placebo controlled trial of nicotinamide in family members at high risk of developing the disease. Impurities present in commercial preparations of nicotinamide were removed by crystallisation use in ENDIT. Data are now available for a total of 1626 years of follow-up on 552 people, half of whom have been taking nic-

otinamide at a dose of 1.2 g/m^2 (maximum 3 g/day). The peak serum concentration obtained with this dose is 100–120 µmol/l which in vivo gives 50 % inhibition of PARP [74]. Compliance will be assessed at the end of the trial by measurement of the urinary metabolite of nicotinamide, 2 pyr, in early morning urine samples taken at 6 monthly intervals [71]. Plasma concentrations of 2 pyr can also be measured [28]. Episodes of mildly abnormal liver biochemistry have been reported in 23 subjects receiving either nicotinamide or placebo and in 14 they resolved spontaneously while the participant continued in the trial on unchanged medication. Of the remainder, 7 are still being monitored and 2 have been withdrawn from the trial. There is no apparent difference in the number of abnormal liver function tests between placebo and nicotinamide groups.

Conclusions

Nicotinamide has been used at pharmacological doses in many people over many years with a low incidence of side effects and toxicity. Safety data have not however been collected in a systematic manner and many older reports failed to distinguish between nicotinamide, nicotinic acid and combined vitamin regimens containing nicotinamide. More recent studies have used purer preparations of nicotinamide and toxic effects have been mild and infrequent. In most situations nicotinamide has been used up to a maximum dose of 3.5 g/day but higher doses (6 g/day) used in combination with radiotherapy and carbogen breathing do result in nausea [69]. We have noted a single report of severe but reversible hepatotoxicity in a patient taking 9 g/day of nicotinamide [34]. Hepatic toxicity has occurred in patients taking sustained release formulations of nicotinic acid in dosages of 3 g/day or more [72] although more recently a long-term study of extended release nicotinic acid has found that it is safe when given in dosages of 3 g/day or less [73]. Nicotinic acid combined in a wax matrix vehicle for sustained release has also been shown to be safe with an improved side effect profile [5]. This wax matrix method of producing sustained release tablets is similar to the sustained release nicotinamide preparation used in ENDIT.

Nicotinamide has no teratogenic or oncogenic effects when given alone but has been noted to potentiate the oncogenicity of streptozotocin, although at doses much higher than those used for human studies. It affects growth in rodents but there is no evidence that it has adverse effects on growth in children. The previous literature provides considerable evidence that nicotinamide is a safe therapy to use when given at adult doses of no more than 3 g/day. After careful review of available data the ENDIT study was started in 1994 [74]. Nicotinamide or placebo have been giv-

en in double blind fashion at doses of up to 3 g/day and are well tolerated in the few side effects. the results of ENDIT will be reported in 2003. Should nicotinamide prove efficacious in diabetes prevention, experience to date suggests that the ratio of risk to benefit of long-term treatment would be highly favourable. Long-term surveillance of the study cohort will however be undertaken whatever the outcome of the trial. Until then we continue to advocate caution regarding the unsupervised use of nicotinamide obtained "over the counter". Higher doses of nicotinamide should still be considered as having toxic potential.

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