



Niacinamide

Introduction

Niacinamide, also known as nicotinamide, is a water-soluble amide of nicotinic acid. Niacinamide is one of two principal forms of the B-complex vitamin, B3. Niacin was first isolated from rice bran in 1911. Niacinamide, the amide of niacin, was later isolated in 1934 by Warburg and Christian when coenzyme II, NADP, was extracted from horse erythrocytes.¹ While niacinamide and niacin have identical vitamin activities (i.e., they both prevent development

of the vitamin B3-deficiency condition, pellagra), they have very different pharmacological activities.

Biochemistry

The structure of niacinamide consists of a pyridine ring with an amide group in position three. Niacinamide is a component of nicotinamide adenine dinucleotide (NAD), also known as coenzyme I, and nicotinamide adenine dinucleotide phosphate (NADP), also known as coenzyme II. These coenzymes are involved in many intracellular oxidation-reduction reactions. They participate in hydrogen transfer reactions, functioning as hydride ion carriers of biological systems.

Pharmacokinetics

The pharmacokinetics of niacinamide depend on dose, species, gender, and route of administration.² Niacinamide is readily absorbed from all parts of the gastrointestinal tract.³ A negligible portion of niacinamide is metabolized to niacin, mostly due to bacterial activity.⁴ Peak serum concentrations are reached in humans within one hour of oral ingestion of standard preparations.⁵ Niacinamide is rapidly cleared from the circulation and distributed in all tissues. It has a high hepatic excretion ratio and plasma clearance can be reduced in patients with hepatic insufficiency.⁶

Mechanisms of Action

Niacinamide acts as an antioxidant by preventing NAD depletion during DNA repair by inhibiting poly (ADP-ribose) polymerase (PARP), which also modulates major histocompatibility complex (MHC) class II expression. Niacinamide inhibits free radical formation and facilitates beta-cell regeneration *in vivo* and *in vitro*.^{7,8} Additional protection from macrophage toxins may be involved in prevention of type 1 diabetes.⁹ Specifically, niacinamide has been shown, via PARP inhibition, to protect pancreatic islet-cell lysis after exposure to oxygen free radicals¹⁰ and nitric oxide.^{11,12} Niacinamide has also been found to stimulate GABA receptors, without binding to the receptor sites, thus creating a benzodiazepine-like effect.¹³

Anti-inflammatory action affecting neutrophil chemotaxis has been reported for niacinamide.¹⁴ Additionally, due to its inhibition of ADP-ribosylation, niacinamide has been shown to suppress cytokine-mediated induction of nitric oxide synthase in a number of cells, thus effecting interleukin-1-exposed chondrocytes, resulting in decreased inflammation.¹⁵

Deficiency States

Pellagra, a disease consisting of bilaterally symmetrical lesions on both sides of the body and hands, occurs as a result of a niacin deficiency. The disease is characterized by hyperpigmentation and thickening of the skin, inflammation of the tongue and mouth, and digestive disturbances including indigestion, anorexia, and diarrhea. In late stages of the disease, irritability, amnesia, and delirium occur.

Clinical Indications

Diabetes

The time of diagnosis of type 1 diabetes is crucial for the potential success of any intervention. Early diagnosis is associated with higher residual C-peptide secretion and a better chance of clinical remission.¹⁶ Treatment with high-dose niacinamide has been shown to exert protective effects on beta-cell function in humans. In a recent meta-analysis, 10 randomized, controlled trials were analyzed. A combined analysis of 158 niacinamide-treated and 129 control patients with recent-onset type 1 diabetes revealed significantly better preservation of basal C-peptide secretion in the niacinamide-receiving cohort after one year. Sub-analysis of the five placebo-controlled trials yielded the same result.¹⁷

There are studies that show no beneficial effect of niacinamide in terms of clinical remission of type 1 diabetes. The patients enrolled in negative studies were diagnosed with diabetes between the ages of 10 and 15, suggesting increased insulin resistance, occurring during and around the time of puberty, may be the reason for a lack of positive outcome using niacinamide in this population.¹⁸⁻²⁰

Niacinamide has been used successfully to prevent or delay the onset of type 1 diabetes among high-risk individuals, defined by high islet-cell antibodies and family history of type 1 diabetes. In a New Zealand study of 80,000 children, 5-7 years old, 20,000 were screened for islet-cell antibodies.²¹ The 150 children with positive islet-cell antibodies received niacinamide therapy. The incidence of type 1 diabetes in the treated group was eight per 100,000/year, well

below the rate of 15-20 per 100,000/year observed among the 60,000 children who were not screened or subsequently treated.

Currently, the European Nicotinamide Diabetes Intervention Trial (ENDIT), begun in 1993, is investigating 40,000 first-degree relatives of type 1 diabetic patients, age 4-40 years. All individuals will be followed to endpoints of type 1 diabetes or for five years free of frank disease with a prediction of 50 percent efficacy. The study will be completed in 2003.²²

The Deutsche Nicotinamide Intervention Study (DENIS) also evaluated the clinical efficacy of high-dose niacinamide in children at high risk for type 1 diabetes. Individuals at risk for developing type 1 diabetes within three years were identified by screening of siblings (age 3-12 years) of patients with type 1 diabetes. They were assessed for the presence of a high islet-cell antibody titer and further randomized into placebo and niacinamide (slow release, 1.2 g) groups. Rates of diabetes onset were similar in both groups throughout the observation period – a maximum of 3.8 years and a median of 2.1 years.²³

Treatment with niacinamide appears to delay rather than completely reverse disease development in those with pre-existing type 1 diabetes. However, treatment of “at risk” groups, in the majority of studies, shows promise in disease prevention.

Schizophrenia

Niacinamide and niacin have been used since 1940 or earlier to treat a number of psychiatric conditions. Hoffer is a strong advocate of the use of niacinamide in the management of schizophrenia and has collected data on more than 1,000 patients given either niacinamide or niacin (1.5-6 g/day) for three months to five years duration.²⁴ Hoffer concluded in further studies that this treatment is most effective for early and acute schizophrenics, while it appears to be ineffective, especially when given alone, for chronic sufferers.²⁵ A study by Mohler found niacinamide to produce an anti-anxiety effect equivalent to a highly potent benzodiazepine. Like benzodiazepines, niacinamide appears to stimulate GABA receptors without binding to receptor sites.¹³

It has also been presumed that patients with sub-clinical pellagra, who have developed perceptual changes and neurasthenia, could be labeled as schizophrenic and would benefit from treatment with niacinamide.²⁶ Treatment remains controversial as both positive²⁷ and negative²⁸ double-blind studies appear in the literature.

Arthritis

For the past five decades Kaufman has written extensively about clinical experience treating joint dysfunction with megadoses of niacinamide, found to be particularly effective for degenerative arthritis of the knee. Kaufman's work in this regard had its roots in the chance observation that joint dysfunction improved in arthritic patients using frequent high doses of niacinamide. Using an index of joint range of motion, the outcome of 455 patients receiving 1,500-4,000 mg (divided doses) of niacinamide daily was measured and compared with results of untreated age-matched control patients.^{29,30} While niacinamide did not appear to have an analgesic effect, pain decreased in the niacinamide-treated group as a result of increased joint mobility. The joint range index usually increased after 1-2 months of treatment.

A double-blind study has substantiated Kaufman's findings. Three months following administration of 3,000 mg/day niacinamide for 12 weeks, compared to patients who received placebo, treated patients had significant improvement in joint mobility and overall severity of arthritis. The treated group showed a decrease in erythrocyte sedimentation rate and was able to reduce anti-inflammatory medication by 13 percent.³¹

Dermatological Conditions

Niacinamide has been used to treat several types of dermatological pathologies.^{32,33} In a review of treatments for bullous pemphigoid, treatment with a niacinamide/tetracycline combination showed promising results compared to other treatment effectiveness and side effects.³⁴ In addition, niacinamide has been used successfully in the treatment of other blistering skin diseases when used in conjunction with tetracycline.³⁵

Niacinamide has also been shown to be effective in the treatment of cutaneous hyperpigmentation, which occurs in multiple conditions. In clinical trials, a five-percent niacinamide moisturizer provided 35-68 percent inhibition of melanosome transfer from melanocytes to keratinocytes, proving to be an effective skin-lightening agent.³⁶ Further studies to investigate the use of niacinamide in regulating melanocyte-keratinocyte interactions are underway.³⁷

Radiation Sensitivity

Animal studies found simultaneous supplementation of niacinamide with radioactive iodine treatment of hyperthyroid goiter increased effectiveness of radiation at lower doses due to niacinamide's radiosensitization.³⁸ A review of clinical research on radiation in cancer therapy has confirmed niacinamide's ability to increase tissue sensitivity to radiation.³⁹

Drug-Nutrient Interactions

Concomitant use of niacinamide and anti-epileptic drugs, specifically carbamazepine, diazepam, and sodium valproate, apparently potentiates the anticonvulsant action of these drugs.⁴⁰ In addition, niacinamide may decrease clearance of carbamazepine when used simultaneously.⁴¹

Side Effects and Toxicity

Because the literature on niacinamide spans more than 50 years, evaluation of toxicity is conflicting. Data on the side effects of niacinamide and niacin are often confused as earlier studies used mixtures of the two in preparations. Furthermore, the purity of niacinamide preparations varies considerably as some preparations include trace amounts of niacin.⁶

Older clinical studies report relatively frequent liver enzyme abnormalities;⁴² however, recent studies using purified niacinamide have not detected such abnormalities.^{17,23} Nausea is usually the first side effect noted with niacinamide. Other side effects associated with high-dose niacinamide include heartburn, vomiting, flatulence, and diarrhea. Mild headaches and dizziness have been reported after giving niacinamide parenterally.⁴³

Dosage

The recommended daily intake (RDA) is 20 mg per day for an adult. The dose used in diabetic and prediabetic individuals ranges from 1.75-3.5 grams per day. In diabetic children, a daily dose of 150-300 mg/year of age, up to 3 grams is often used.⁴⁴ Self medication of high-dose niacinamide should be discouraged.

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