Review

Nicotinamide in dermatology: a capsule summary

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Introduction

Nicotinamide (niacinamide) is the water-soluble, physiologically active amide of vitamin B3, or nicotinic acid (niacin). Nicotinamide is converted into nicotinamide adenine dinucleotide (NAD; coenzyme I) and, subsequently, nicotinamide adenine dinucleotide phosphate (NADP; coenzyme II), which are the coenzymes of countless dehydrogenases. Dehydrogenases supply hydrogen to the respiratory chain for oxidation and energy production.

Nicotinamide, in contrast with niacin, has no effect on the blood pressure, pulse, or body temperature.

It has a wide therapeutic index and is not a teratogen.

Molecular immunopharmacology

Nicotinamide is an inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1), a nuclear enzyme contributing to DNA repair, which, if overactivated, causes cell dysfunction or necrosis. PARP enhances nuclear factor-kB (NF-κB)-mediated transcription, which plays a central role in the expression of cytokines, adhesion molecules, and inflammatory mediators. Nicotinamide inhibits the expression of intercellular adhesion molecule-1 (ICAM-1) and major histocompatibility complex II (MHC-II), and the production of interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), IL-1, and macrophage migration inhibition factor (MIF). It is speculated that MIF inhibition may be responsible for the steroid-sparing effect of nicotinamide, as MIF, in contrast with other cytokines, is upregulated by steroids and overrides the anti-inflammatory effects of these agents.

Nicotinamide’s potent inhibition of phosphodiesterase (PDE) and the resultant increase in cyclic AMP (cAMP) result in the inhibition of the release of proteases from leukocytes and, in addition, the inhibition of lymphocyte transformation.

Nicotinamide blocks mast cell mediator release and inhibits neutrophil and eosinophil chemotaxis.

Nicotinamide scavenges oxygen radicals, but not nitric oxide; however, it inhibits nitric oxide synthase mRNA induction.

Dermatologic applications of systemic nicotinamide

There have been some anecdotal reports on the use of oral nicotinamide per se in the treatment of dermatitis herpetiformis, generalized granuloma annulare, necrobiosis lipoidica, and bullous pemphigoid. Nicotinamide plus tetracycline have been used in the treatment of erythema elevatum diutinum, linear IgA dermatosis, pemphigus, cicatricial pemphigoid, and lichen planus pemphigoides.

In the treatment of bullous pemphigoid, a nicotinamide–tetracycline combination offers the rapid clearance of lesions in 2–3 weeks. The percentage of nonresponders in generalized disease is below 10% and in localized disease around zero. The daily doses of tetracycline and nicotinamide vary between 1 and 2 g and 1.2 and 2 g, respectively, with a preferred dose of 1.5 g.

In the treatment of cicatricial pemphigoid, a nicotinamide–tetracycline combination has shown benefit even in extensive or long-standing cases that have been inadequately managed with immunosuppressive agents. This regimen is worthwhile for the treatment of cicatricial pemphigoid because the disease responds only partly and temporarily to any therapy.

A nicotinamide–tetracycline combination is a useful steroid-sparing regimen in the treatment of pemphigus vulgaris.
Nicotinamide has been used for the treatment of discoid lupus erythematosus (DLE) in dogs. Nicotinamide is angiogenic and has been shown to accelerate wound healing and skin flap survival in animal studies. Nicotinamide has an anti-inflammatory effect on erythema in guinea pigs induced by nitrogen mustard exposure. Nicotinamide enhances the effect of methotrexate (MTX) on murine models of arthritis, whilst decreasing the hepatotoxicity of this agent. A nicotinamide–MTX combination may prove to be a potent treatment of psoriatic arthritis. Nicotinamide increases tissue sensitivity to radiotherapy and is useful in cancer therapy. Nicotinamide in combination with zinc, an immunomodulator, is being assessed in clinical studies for the treatment of inflammatory skin diseases, such as bullous pemphigoid and acne vulgaris.

Dermatologic applications of topical nicotinamide

Atopic dermatitis
In a study on 28 patients, 2% nicotinamide cream significantly decreased transepidermal water loss (TEWL) and was more effective than white petrolatum as a moisturizer. Nicotinamide stimulates the synthesis of ceramides, free fatty acids, and cholesterol, and improves the epidermal permeability barrier.

Rosacea
A randomized, investigator-blind, controlled study on 50 patients showed that a nicotinamide-containing facial moisturizer improved the skin barrier and benefited subjects with rosacea.

Acne
In a multicenter trial, a 4% topical preparation of nicotinamide gave a global reduction in acne of 82%, compared with 68% for 1% clindamycin gel, over an 8-week period, with the additional advantage of avoiding antimicrobial resistance. This difference was not statistically significant. A recent study performed in India showed no added advantage of clindamycin phosphate 1% in combination with nicotinamide gel 4% over clindamycin phosphate 1% alone.

Excess sebum
In vitro studies have shown a dose-dependent inhibition of sebocyte secretions by nicotinamide.

Hyperpigmentation
Nicotinamide cream 5% significantly decreased hyperpigmentation compared with vehicle alone after 4 weeks of use. Moreover, the addition of 2% nicotinamide to a sun protection factor 15 (SPF 15) sunscreen led to significant lightening of the skin compared with sunscreen alone after 4 weeks of use.

Nicotinamide prevents the transfer of melanin from melanocytes to keratinocytes, and also the UV-A-induced proliferation of melanocytes.

Skin aging
In a double-blind, placebo-controlled trial, a 5% nicotinamide cream applied for 12 weeks significantly reduced yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. Nicotinamide’s anti-aging action is exerted by an increase in NADH and NADPH, which are antioxidants capable of inhibiting glycation, and by an increase in the production of collagen and a decrease in the production of glycosaminoglycans. Nicotinamide also increases the production of the epidermal proteins keratin, filaggrin, and involucrin.

Light damage
In vivo studies in mice showed an inhibition of photocarcinogenesis and photo-immunosuppression by nicotinamide. In human studies, nicotinamide prevented UV immunosuppression and allowed the development of a Mantoux response after UV exposure.

Maintenance of resurfacing
Nicotinamide functions as a mild exfoliant by speeding up epidermal turnover and maintaining a smooth skin surface in sensitive skin immediately after healing has occurred with the resurfacing procedure. Some experts prefer nicotinamide to hydroxy acid or salicylic acid exfoliants in the immediate post-resurfacing period.

Antimicrobial and anti-leishmanial activity of nicotinamide
Both in vivo and in vitro studies have demonstrated the mild activity of nicotinamide against Mycobacterium tuberculosis and human immunodeficiency virus (HIV). The antimycobacterial activity of nicotinamide is exerted through the inhibition of the class III NAD-dependent deacetylase family of proteins [the silent information regulatory 2 (Sir2) protein family], and its anti-HIV effect through the inhibition of PARP.

In vitro studies have shown the activity of nicotinamide against Leishmania major as a result of its inhibition of Sir2.

Proposals for future research
As nicotinamide prevents the transfer of melanin from melanocytes to keratinocytes, functions as a mild exfoliant and exerts an anti-inflammatory effect, its combination with tyrosinase inhibitors kojic acid and hydroquinone could provide a synergistic whitening effect, with the additional benefit of mitigating against the inflammation induced by these agents (Namazi Formulae).
As nicotinamide prevents the UVA-induced proliferation of melanocytes, a nicotinamide-containing sunscreen may be of value for individuals presenting with increasing eruption of facial nevi, for which no effective preventative measure currently exists.

As nicotinamide can inhibit photocarcinogenesis and photo-immunosuppression, nicotinamide-containing sunscreens may be of particular value in Australasian countries and in cancer-provoking conditions, such as Gorlin’s syndrome and xeroderma pigmentosum.

Nicotinamide may exert a direct inhibitory effect on *Propionibacterium acne* as a result of its inhibition of Sir2 enzymes.

**Acknowledgements**

This work was supported by PHARMALINES – Middle East.

**References**
