Topical N-acetylcysteine for lamellar ichthyosis

Pedro Redondo, Ana Bauzá

The antioxidant N-acetylcysteine has an antiproliferative effect on a culture of human keratinocytes. We report a patient with lamellar ichthyosis satisfactorily treated with topical N-acetylcysteine.

Topical therapy of ichthyosis consists of emollient creams, ointments, and bath oils. In addition, keratolytic agents such as α-hydroxy acids, propylene, and urea preparations can produce some improvement. Topical retinoids have been shown to help, although they should be used cautiously to avoid irritation. N-acetylcysteine (NAC) is a thiol that reacts with reactive oxidative intermediates and replenishes the intracellular cysteine necessary for the production of glutathione, an endogenous antioxidant.[1]

Cultures of keratinocytes were prepared from the skin of human female breast.[2] To examine the effect of NAC on cell proliferation, second-passage keratinocytes were incubated under serum-free, low-calcium conditions, with 0·5–30 mmol/L NAC and cell numbers determined. NAC dose-dependently suppressed the incorporation of ^{3}H-thymidine in keratinocytes (figure 1). Median inhibitory concentration for NAC was 10 mmol/L, and the inhibitory effect of NAC was time dependent (data not shown). Cell viability as determined by trypan-blue exclusion assay and propidium-iodide staining indicated that 95% of cells were viable after incubation with 20 mmol/L NAC for 3 days. Inhibition of keratinocyte proliferation by NAC is therefore not due to the cytotoxic effect of this drug.

A 33-year-old woman with lamellar ichthyosis had been treated for 2 years with 30 mg acitretin daily and topical urea lotions. She presented large and dark scales with a dirty appearance particularly on the trunk, limbs, scalp, and neck. A water-in-oil emulsion containing 10% NAC (Sigma, Madrid, Spain) was prepared. Placebo consisted of the same emulsion without NAC. She was instructed to apply each preparation twice daily on the skin of opposite forearms (initially randomly selected). Preparations were applied without occlusion and followed thoroughly. 5 weeks later, there was outstanding improvement. No changes were observed in placebo-treated areas (figure 2).

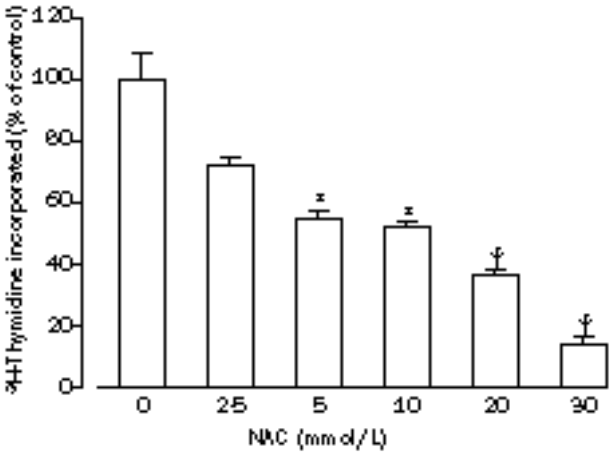

Figure 1: **Effect of NAC on ^{3}H-thymidine uptake**
Human keratinocytes cultured in 96-well plates were incubated with various concentrations of NAC for 24 h, and labelled successively with 1 μCi/mL of ^{3}H-thymidine for 6 h. At the end of the incubation period, ^{3}H-thymidine incorporation was determined. The results are presented as the proportion of the control in the absence of NAC. Each value is the mean (SD) of three separate experiments. Each experiment included three to six wells in each treatment group. *p<0·01; †p<0·001 compared with controls.

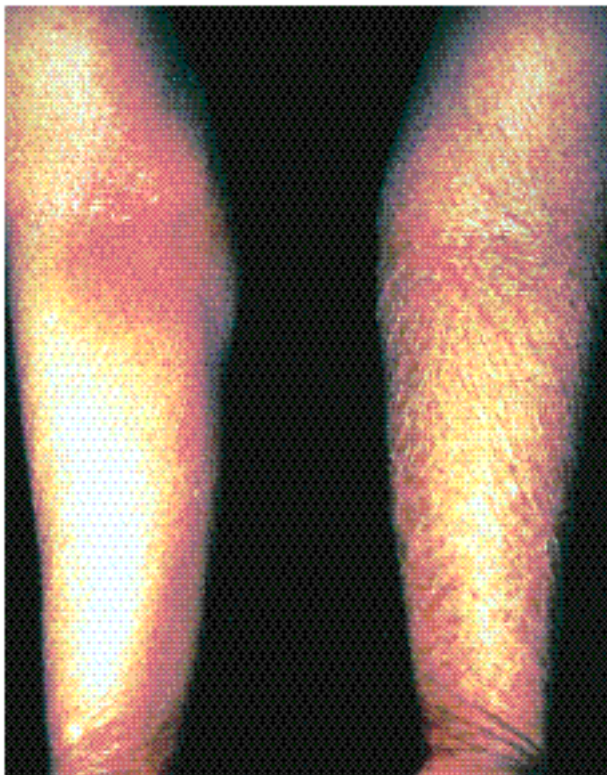

Figure 2: **Appearance in patient treated for 5 weeks**
One forearm (left) received topical NAC, whereas the other (right) received placebo.

NAC has been used as a mucolytic agent in various pulmonary disorders and as an antidote for acetaminophen overdose.[1] Lamellar ichthyosis is a congenital disorder, associated with a greatly increased epidermopoiesis.[3] The dermatological usefulness of NAC has not been previously reported, although topically applied NAC can prevent skin irritation resulting from radiotherapy[4] and protects from sun-induced erythema. NAC is labile and tends to break down, releasing sulphur-containing compounds. The water-in-silicone emulsion improves stability and reduces malodour. Recent studies show that NAC suppresses proliferation of NIH3T3 fibroblast cells, and this antiproliferative effect is mediated by reversible blocking cell-cycle progression in G1 phase.[5] Because NAC is an atoxic and hypoallergic aminoacid derivative with successful therapeutic uses and rare side-effects, it may be useful in the treatment of hyperproliferative skin disorders.

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Department of Dermatology, University Clinic of Navarra, School of Medicine, 31080 Pamplona, Spain (P Redondo MD, A Bauzá MD)

Correspondence to: Dr Pedro Redondo
(e-mail: predondo@unav.es)