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Successful Treatment with Topical N-Acetylcysteine in Urea in Five Children with Congenital Lamellar Ichthyosis

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Abstract: **We reported the efficacy of topical cutaneous N-acetylcysteine in children with type I lamellar ichthyosis. The drug was applied on predetermined body surface areas two times a day for 6 weeks, followed by a daily maintenance application. During the first 2 weeks of treatment, a significant improvement occurred. After 4 months of maintenance application, a marked overall improvement occurred in all the treated areas. Only two patients showed mild adverse effects such as light burning, pruritus, and irritation. Even though a larger group of patients should be necessary to confirm the data, topical 10% N-acetylcysteine emulsion prepared in urea 5% seems to be a valuable and safe therapeutic option for lamellar ichthyosis in children, with benefit not only for skin lesions but also for ectropion avoiding a surgical procedure.**

Lamellar ichthyosis is a genetically heterogeneous group of disorders of keratinization that is generally inherited in an autosomal recessive fashion (1).

Current treatments for lamellar ichthyosis primarily consist of topical keratolytic agents and emollients. If ichthyosis cannot be controlled by topical therapy alone, retinoids may be used (2,3). Although a permanent cure for lamellar ichthyosis is not available, we describe herein a palliative treatment that is efficient and well tolerated for patients with this entity. We report five children with lamellar ichthyosis successfully treated with topical N-acetylcysteine (NAC) in urea with a maximum 4-year follow-up.

CASE REPORT

Five patients (Table 1) had previously been treated with emollient creams containing lactic acid, salicylic acid, and 5% urea with poor results. We prepared a new topical emulsion mixing 10% N-acetylcysteine and 5% urea (N-acetylcysteine [96 gr], URECREM HYDRO: Ethicus [960 csp]). The organoleptic characteristics included a white-ocher (W/O) emulsion of light consistency with a strong sulphuric smell, which could be tempered with an essence. Conservation conditions were complied using airtight bottles, which were protected from light and stored in a cool, dry place.

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TABLE 1. *Patients Treatment and Evolution*

Patient	Sex/Age (yrs)	FU (yrs)	Treatment	Adverse effects	Response	Associated abnormalities
1	F/16	3	Acitretin 0.5 mg/kg/d 10% N-acetylcysteine in 5% urea	–	Successful	–
2	F/12	3	Emollients 10% N-acetylcysteine in 5% urea	–	Successful	–
3	F/2	2	Emollients 10% N-acetylcysteine in 5% urea	Initial irritation	Successful partial resolution of ectropion	Coeliac disease (probable)
4 (Figs. 1–3)	F/5	4	Emollients 10% N-acetylcysteine (legs/arms), 5% N-acetylcysteine in 5% urea (face/body)	Initial irritation	Excellent resolution of ectropion	Coeliac disease
5 (Figs. 4–6)	M/1	1	Emollients 10% N-acetylcysteine in 5% urea	–	Successful	–

FU, follow up.

The emulsion has no preservatives, so it must be prepared monthly.

It is advisable to apply the emulsion after bathing. The parents were instructed to apply a thin layer of each preparation twice daily on the skin of the face, neck, torso, and arms. On the lower limbs and buttocks, they used a water-in-oil emulsion containing only urea 5% (placebo). Preparations were applied without occlusion, and patients were followed up thoroughly for 6 weeks.

After the first week of treatment, partial improvement was noted, and over the next 7 days, further reduction in scaling was observed on the N-acetylcysteine emulsion-treated areas. After 6 weeks, the use of preparations was reduced to a single daily application. Four months later, a marked overall improvement was seen in symptoms. In Figs. 1–6, we show the positive results obtained after use of the emulsion. One of the patients was instructed to apply the NAC preparation twice daily on her left thigh and placebo twice daily on her right thigh. We could see outstanding improvement (left thigh), without changes in placebo-treated areas (right thigh) (Fig. 7).

No systemic side effects were recorded during the treatment, and no changes in lab results occurred in the routine tests performed by the pediatricians—hemogram, liver, and urine test, and in patient 4 the specific test for celiac disease.

Only two patients exhibited localized skin reactions when they began the medication. One patient had mild pruritus, which resolved after a few days of continued treatment. The second patient had burning and irritation, and these symptoms regressed a few days after tapering N-acetylcysteine to 5% on the facial application. Then, the patients continued applying the emulsion to their whole body, including the eyelids, external auditory canal, and genital areas, without any irritation as long as the skin had no fissures.

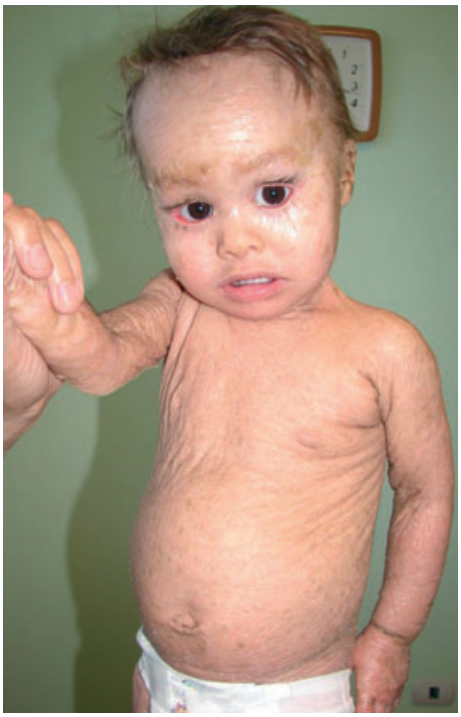

Figure 1. Large dark plate-like scales and ectropion before treatment.

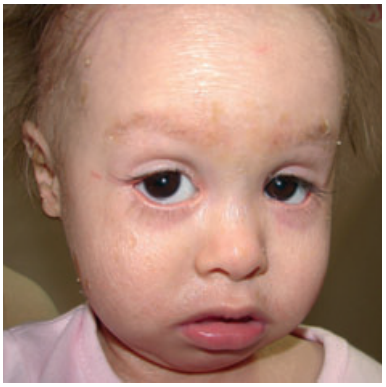

Figure 2. Improvement of topical N-acetylcysteine areas after 6 weeks of treatment.

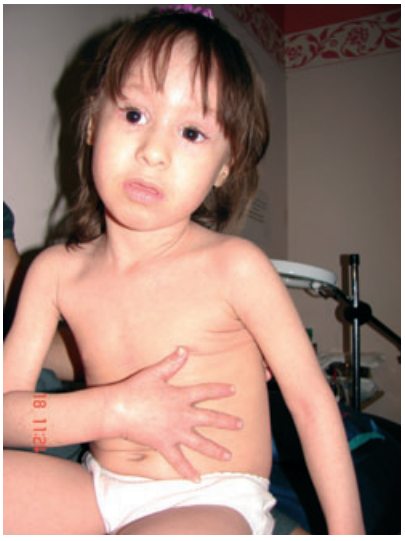

Figure 3. Four years after topical N-acetylcysteine treatment.

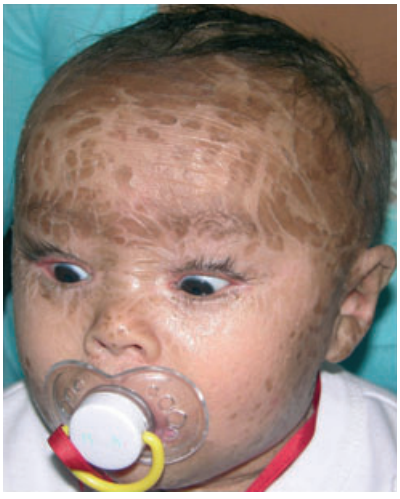

Figure 4. Large brown scales on face and scalp.

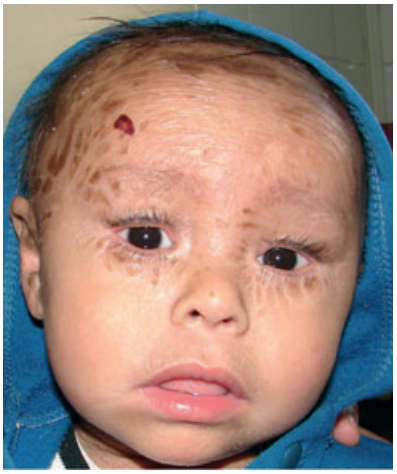

Figure 5. Six weeks after treatment.

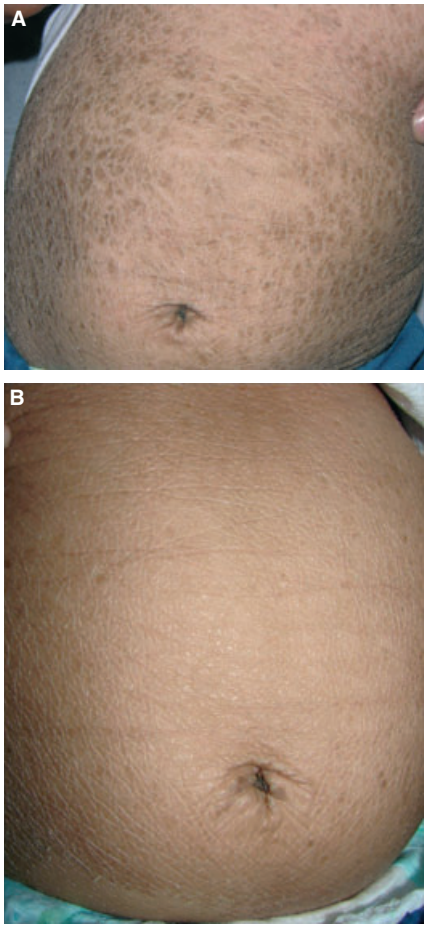

Figure 6. (**A**) Intense dryness and scaling with large, brown, plate-like scales covering the trunk. (**B**) Improvement of N-acetylcysteine treated areas after 6 weeks of treatment.

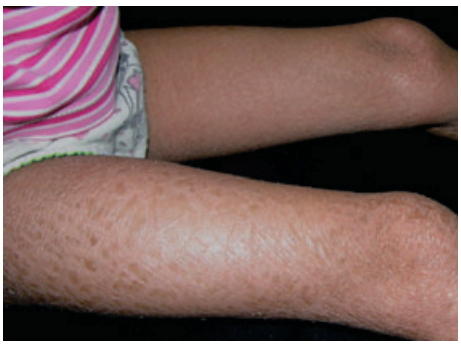

Figure 7. Appearance of patient treated for 4 weeks. One thigh (left) received topical NAC in urea 5%, whereas the other (right) received placebo (urea 5% only).

DISCUSSION

Lamellar ichthyosis is a rare disease of the subgroup of nonsyndromic autosomal recessive congenital ichthyosis (ARCI) characterized by nonbullous hyperkeratosis with facial and body surface involvement presenting with thick hyperkeratotic scales, severe dryness, and variable skin redness.

Treatment of lamellar ichthyosis is based on disease severity, although a permanent cure may not yet be possible. Treatment options for lamellar ichthyosis include topical formulations and oral retinoids (2).

Topical treatment of ichthyosis has classically included generous and frequent applications of emollient creams, ointments, keratolytic agents, and bath oils. Numerous commercially available formulations of keratolytic agents exist, including α-hydroxy acids (lactic acid and glycolic acid), tazarotene, tacrolimus, salicylic acid, urea, and propylene glycol. In addition, many dermatologists prescribe keratolytic treatments that they have formulated according to their own preparations (2,3,5,6). However, any topically applied agent will be transcutaneously absorbed to a much higher degree than through normal skin. These patients with lamellar ichthyosis have a reduced barrier function with increased transepidermal water loss values. Their increased skin permeability may result in intoxication by cutaneous absorption of substances applied to the skin (e.g., irritability, agitation, myoclonia, difficulty in walking, and lactic acidosis as a result of excessive application of emollients containing lactic acid; fever, hyperpnoea with respiratory alkalosis, comatose state, and oculogyric crisis after topical application of salicylic acid (1,7,8)). The literature reports poisoning and toxic effects of many topical drugs in patients with ichthyosis related principally to excessive applications rather than the indicated amount or the patient's use of concomitant drugs.

The first case of an adult with lamellar ichthyosis successfully treated with topical N-acetylcysteine was reported by Redondo and Bauzá in 1999 (9). Since then, only two authors have reported successful treatments with topical N-acetylcysteine in children with congenital ichthyosis (10,11).

N-acetylcysteine is a thiol derivative that has traditionally been used as a mucolytic, antioxidant, nephroprotective agent and as an antidote for acetaminophen toxicity. Topically applied, NAC may prevent radiotherapy-induced cutaneous irritation and protection from solar erythema. N-acetylcysteine is an atoxic and hypoallergic amino acid derivative with successful therapeutic uses and rare side effects like mild pruritus, irritation, and burning sensation. The bioavailability is $< 3\%$ in the topical form, with hepatic metabolism and renal excretion. Nausea, vomiting, anaphylactoid reactions, urticaria, and angioedema are rare side effects reported in the literature, and are more common among asthmatic or atopic patients with infusions or oral NAC.

The inhibitory effect of this drug on proliferation of NIH3T3 fibroblast cells has been demonstrated, and its antiproliferative effect is mediated by reversible blocking of cell-cycle progression in G1 phase, but not by its cytotoxic effect (9). The inhibition of keratinocyte proliferation by N-acetylcysteine has raised the idea of the dermatologic usefulness of this drug in the treatment of diseases with increased epidermopoiesis (9,10).

Our patients experienced rapid and significant improvement with a water-in-oil emulsion containing 10% N-acetylcysteine plus 5% urea with minimal side effects. We observed that this mixture was more effective than each preparation separately. Five percent urea appears to produce an optimal pharmacologic effect of the active ingredients and transcutaneous penetration.

CONCLUSION

Even though this treatment would need a larger group of patients to confirm the data, topical application of 10% or 5% N-acetylcysteine plus 5% urea emulsion appears to be a valuable and safe therapeutic option in the management of lamellar ichthyosis. This treatment not only provides a great benefit for skin lesions, but also for ectropion, thereby avoiding an unnecessary surgical procedure (10,11).

This is the first report in the literature that studies the long-term, consistent use of this mixture in patients with this entity.

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REFERENCES

1. Vahlquist A, Ganemo A, Virtanene M. Congenital ichthyosis: an overview of current and emerging therapies. Acta Derm Venereol 2008;88:4–14.
2. DiGiovanna J, Robinson-Bostom L. Ichthyosis etiology, diagnosis, and management. Am J Clin Dermatol 2003;4:81–95.
3. Ganemo A, Virtanen M, Vahlquist A. Improved topical treatment of lamellar ichthyosis: a double-blind study of four different cream formulations. Br J Dermatol 1999; 141:1027–1032.
4. Oji V, Ttraupe H. Ichthyoses: differential diagnoses and molecular genetics. Eur J Dermatol 2006;16:349–359.
5. Marulli G, Campione E, Chimenti M et al. Type I lamellar ichthyosis improved by tazarotene 0.1% gel. Clin Exp Dermatol 2003;28:391–393.
6. Kundu RV, Garg A, Worobec S. Lamellar ichthyosis treated with tazarotene 0.1% gel. J Am Acad Dermatol 2006;55(Suppl 5):S94–S95.
7. Allen D, Esterly N. Significant systemic absorption of tacrolimus after topical application in a patient with lamellar ichthyosis. Arch Dermatol 2002;138:1259–1260.
8. Ramirez ME, Youseef WF, Romero RG et al. Acute percutaneous lactic acid poisoning in a child. Pediatr Dermatol 2006;23:282–285.
9. Redondo P, Bauzá A. Topical N-acetylcysteine for lamellar ichthyosis. Lancet 1999;354:1880.
10. Sarici S, Sahin M, Yurdakök M. Topical N-acetylcysteine treatment in neonatal ichthyosis. Turk J Pediatr 2003; 45:245–247.
11. Gicquel J, Vabres P, Dighiero P. Use of topical cutaneous N-acetylcysteine in the treatment of major bilateral ectropion in an infant with lamellar ichthyosis. J Fr Ophtalmol 2005;28:412–415.