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Clinical evidences of urea at low concentration

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Abstract

Urea is a hygroscopic molecule that, because of its moisturising properties, is topically used for the treatment of skin dryness at concentrations ranging from 2% to 12% in different formulations. Based on existing literature, low-concentration urea-containing products are effective in the treatment and/or prevention of xerosis in some skin disorders such as ichthyosis, atopic dermatitis and psoriasis, or unrelated to specific skin diseases. Generally, urea formulations at low concentration are well-tolerated and suited for the treatment of large skin areas, once or twice daily, even for a long period of time. At low concentrations stinging and burning sensation is rare and transient, whit no reported sensitisation despite its widespread use.

1 | INTRODUCTION

Urea is a hygroscopic molecule physiologically present on the skin as a component of the Natural Moisturizing Factor (NMF) that contributes to skin hydration.[1] Because of its moisturising properties, it has been topically used for the treatment of skin dryness at concentrations ranging from 2% to 12% in different formulations. It is effective in the treatment of xerosis associated to ichthyosis, atopic dermatitis and psoriasis.

The aim of this paper is to review the clinical evidences of the uses of urea at low concentration in dermatology. All the studies evaluating the use of urea in skin disorders published in the English literature were analysed. An electronic search was performed using PubMed database using the following keywords: urea [Mesh] AND (skin [Mesh] OR xerosis [Mesh] OR ichthyosis [Mesh] OR dermatitis [Mesh] OR psoriasis [Mesh]). In addition, pertinent references not identified by search engines and retrieved from articles/books were also considered. All studies identified as relevant, including controlled studies, case series, case reports and reviews were analysed.

Most of the available articles concerns the use of urea in ichthyosis, atopic dermatitis and psoriasis, while a few deals with other disorders (Tables 1-3).

2 | ICHTHYOSIS

The term ichthyosis includes a group of genetic disorders of keratinisation characterised by dry and scaly skin. They may cause cosmetic problems and pruritus that, especially in childhood, may be burdensome. Ichthyosis vulgaris, that represents the most common form, is caused by mutations in the filaggrin gene and is clinically characterised by xerosis mainly affecting the extensor surfaces of the limbs and the trunk. Keratosis pilaris, defined by keratotic elevation around hair follicle orifices, is also quite common both on the upper and lower limbs[2] (Figures 1 and 2).

Different studies conducted in adults and in paediatric age have demonstrated the efficacy of topical urea formulations in controlling xerosis related to ichthyosis vulgaris,[2-6] X-linked,[5] and lamellar[5,7] (Table 1). In these studies, urea has been tested at 5%-10% concentration, once or twice daily for 2-8 weeks, alone or in comparison with other topicals. In particular, in ichthyosis vulgaris, that represents the most frequent form of ichthyosis, urea was found to be equally or slightly more efficacious in controlling symptoms than other products such as glycerin,[3] 2% of salicylic acid plus paraffin[4] and retinoic acid.[8] In ichthyosis vulgaris, the effect of urea in skin hydration seems to go beyond the simple hydration, being also related to the regulation of epidermal genes necessary for proper barrier function maintenance, as it may increase filaggrin gene expression.[2,9]

Although generally the efficacy of urea in ichthyoses has been evaluated in terms of clinical outcomes, in a recent study, the good clinical results obtained by an emulsion containing 10% of urea in five patients affected by ichthyosis vulgaris were objectively confirmed by videodermatoscopy and reflectance confocal microscopy showing the reduction/disappearance of scales and

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TABLE 1 Ichthyosis: evidences on the use of urea at low concentrations (trials/case series ≥5 subjects)

Author(s)	Type of ichthyosis	Urea concentration and formulation	Comparator	Number of patients	Treatment(s) schedule	Evaluation	Outcome
Pope et al[4]	Vulgaris X-linked recessive	10% cream	2% salicylic acid ointment, paraffin	37 47	Twice daily for 2 wk	Clinical	Improvement of xerosis
Grice et al[8]	Vulgaris X-linked recessive	10% cream	Base cream, 0.1% retinoic acid	6 6	Twice daily for 3 wk	Water-binding capacity	Improvement
Horii et al[6]	Vulgaris	10% cream	None	5	Four times daily for 2-4 wk	Clinical	Improvement of xerosis
Kuster et al[5]	Vulgaris X-linked recessive Lamellar	10% lotion	5% lactic acid lotion	34 6 11	Twice daily for 8 wk	Clinical	Improvement of xerosis
Tadini et al[3]	Vulgaris	10% lotion	Glycerol-based cream	27	Twice daily for 4 wk	Clinical	Improvement of xerosis
Benintende et al[2]	Vulgaris	10% emulsion	None	5	Twice daily for 4 wk	Clinical and instrumental (videodermoscopy and reflectance confocal microscopy)	Improvement of xerosis. Improvement/normalisation of instrumental parameters
Bassotti, et al[7]	Lamellar	5% emulsion	None	5	Twice daily for 6 wk	Clinical	Improvement of xerosis

TABLE 2 Atopic dermatitis: evidences on the use of urea at low concentrations (trials/case series ≥5 subjects)

Author(s)	Urea concentration and formulation	Comparator	Number of patients	Treatment(s) schedule	Evaluation	Outcome
Pigatto et al[16]	10% cream	Base cream	70	Twice daily for 4 wk	Clinical	Improvement of dryness, itching and erythema
Bohnsack et al[15]	10% lotion	Vehicle cream	41	Twice daily for 4 wk	Clinical; corneometry	Improvement of dryness; increase in skin hydration
Wilhelm et al[17]	10% cream	Vehicle cream	80	Twice daily for 4 wk	Clinical; corneometry	Improvement of itch, erythema, dryness, induration/papules; increase in skin hydration
Lodèn et al[18]	5% cream	None	15	Twice daily for 20 d	Corneometry; TEWL evaluation	Increase in skin hydration; reduction of TEWL
Wirén et al[19]	5% cream	None	22	Twice daily for 6 mo (after a 3-wk treatment with betamethasone valerate 0.01% cream)	Clinical; TEWL evaluation	Reduction of time to relapse; no significant reduction of TEWL
Bissonnette et al[20]	5% lotion	10% urea lotion	100	Twice daily for 42 d	Clinical	Improvement in both groups
Nasrollahi et al[21]	5% emulsion	Linoleic acid emulsion	20	Two to three times daily for 4 wk	Clinical; TEWL and erythema evaluation; corneometry; ultrasound	Clinical and instrumental improvement
Akerstrom et al[13]	5% cream	Base cream	172	Twice daily for 180 d	Clinical	Reduction of time to relapse

TABLE 3 Psoriasis and other disorders: evidences on the use of urea at low concentrations (trials/case series ≥5 subjects)

Author(s)	Disorder	Urea concentration and formulation	Comparator	Number of patients	Treatment(s) schedule	Evaluation	Outcome
Fredriksson et al[29]	Psoriasis	12% cream	Base cream	40	Twice daily for 1 wk	Clinical	Improvement of scaling
Hagemann et al[30]	Psoriasis	10% ointment	Vehicle or no treatment	10	Three times daily for 2 wk	Clinical; corneometry; TEWL; histopathology	Improvement of scaling, erythema and induration; increase of skin hydration; reduction of epidermal thickness and proliferation
Horii et al[6]	Senile xerosis	10% cream	None	10	Four times daily for 2-4 wk	Clinical	Improvement of xerosis
Castello et al[32]	Xerosis in hemodialysed patients	10% lotion	None	15	Twice daily for 4 wk	Clinical	Improvement of xerosis and pruritus
Gisoldi[33]	Xerosis	10% cream	12% ammonium lactate	36	Twice daily for 3 wk	Clinical, TEWL	Improvement of xerosis and reduction of TEWL
Pham et al[35]	Xerosis of the feet in diabetic patients	10% cream and 4% lactic acid	Base cream	40	Twice daily, for 4 wk	Clinical	Improvement of xerosis
Ren et al[37]	Sorafenib-induced hand-foot skin reactions	10% cream	None	439	Three times a day for up to 12 wk	Clinical	Usefulness in prevention
Lodén et al[38]	Hand eczema	5% cream	None	26	Twice daily	Clinical	Usefulness in prevention of relapses
Tanuma et al[34]	Combination with topical lanoconazole in tinea pedis	10% ointment + 1% lanoconazole cream	1% lanoconazole cream	23	Once daily for 12 wk	Clinical	Enhanced efficacy of lanoconazole

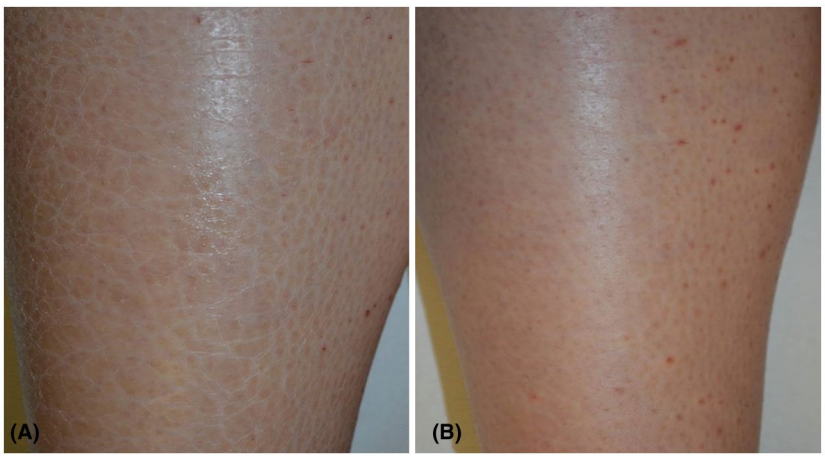

FIGURE 1 Severe xerosis of the leg in a patient with ichthyosis vulgaris at baseline (A) and after 4 weeks of treatment with 10% urea cream (B): excellent response

the improvement/normalisation of furrow's size and morphology, respectively.[2]

The use of topical urea preparations in ichthyoses has resulted in a good safety profile, as only occasional mild burning or irritation have been reported.[10]

3 | ATOPIC DERMATITIS

Atopic dermatitis is a common chronic-relapsing inflammatory skin disease mainly affecting children and characterised by intense itching, dry skin and eczema. Skin barrier dysfunction is characteristic of

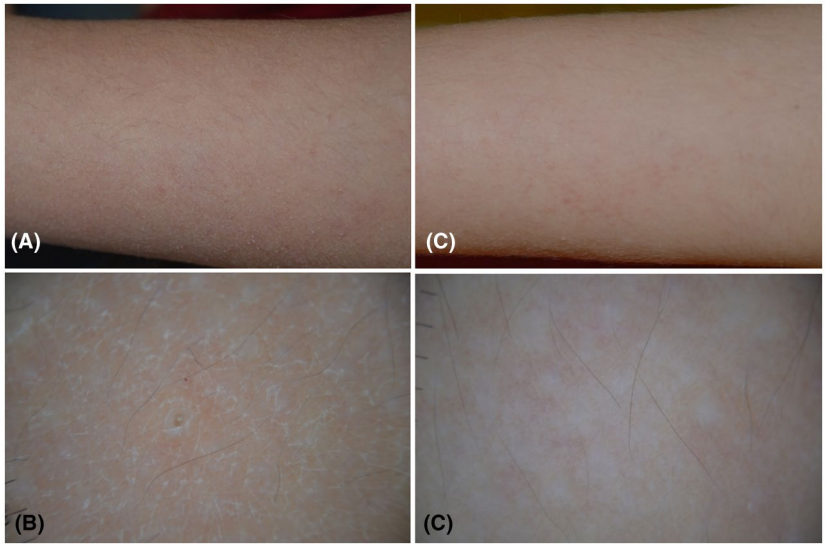

FIGURE 2 Clinical (A and C) and dermoscopic (x10) (B and D) aspect of keratosis pilaris of the arm in a patient affected by atopic dermatitis at baseline (A and B) and after 4 weeks of treatment with 10% urea lotion (C and D): excellent response

the disease, facilitating the entry of allergens. Persistent inflammation may in turn impair barrier function.[1,11] For this reason, skin barrier restoration represents the mainstay of the treatment of atopic dermatitis and the use of moisturisers is recommended by several international guidelines.[12] Moisturisers, alone or in combination with pharmacological treatments, are able to improve disease severity, increase the time of relapse and reduce the time of flares.[13,14]

Moisturisers containing urea show a great evidence of efficacy in atopic dermatitis, being supported by several clinical trials in adults and children[14-22] (Table 2). They have also demonstrated to improve stratum corneum hydration, water-binding capacity and transepidermal water loss (TEWL) of eczematous skin.[10,23] In some trials, the use of urea in atopic dermatitis has been studied combined with topical corticosteroids such as hydrocortisone or betamethasone-17-valerate, these combination therapies being more effective than treatment with corticosteroids alone.[24-26]

Urea-based moisturisers may also reduce the risk of eczema relapse. In a study, maintenance treatment with 5% urea cream on previous eczematous areas showed to reduce the risk of relapse to approximately one-third compared with the area not treated.[19]

Occasional side effects observed in atopic dermatitis during treatment with urea-based products are represented by stinging and burning.[13]

4 | PSORIASIS

As known, hyperkeratotic lesions of psoriasis are best managed by high-concentration urea products.[27,28] However, a few studies suggested that also low concentrations (from 5% to 12%) may have some benefits and may be used as a safe basic therapy leading to increased patient satisfaction[28-30] (Table 3). In one study, on 10 psoriatic patient, plaque type lesions were treated for 2 weeks with an ointment containing 10% of urea, with significant improvement of clinical score (scaling and induration), hydration of the stratum corneum and TEWL, and reduction in epidermal thickness and proliferation.[30] Moreover, evidence exists for an enhanced efficacy of pharmacological topical agents such as betamethasone dipropionate and calcipotriol.[28,31]

5 | OTHER USES

Some clinical trials support the efficacy of urea also in the treatment of xerosis unrelated to specific skin diseases (Table 3). Common study endpoints are represented by clinical assessment and instrumental evaluation of TEWL and stratum corneum hydration.[10,32,33] In an open pilot trial, topical 10% urea plus dexpanthenol lotion significantly improved skin dryness and pruritus in dialysed patients with an excellent tolerability.[32]

In another study, a 10% urea ointment has demonstrated to improve the efficacy of topical lanoconazole in the treatment of hyperkeratotic type tinea pedis.[34]

The regular use of a moisturiser containing 10% of urea and 4% of lactic acid has demonstrated to be beneficial in the treatment of moderate-to-severe xerosis of the feet in patients with diabetes.[35] This is particularly important as, in these patients, xerosis generally increases the risk of complications, including infection and ulceration.[35,36]

In a randomised, open-label trial on 871 patients with advanced hepatocellular carcinoma, starting sorafenib treatment, the prophylactic use of a 10% urea-based cream reduced sorafenib-induced hand-foot skin reactions and improved patient quality of life.[37]

In another study on 53 patients with successfully treated hand eczema, the application of a 5% urea emulsion significantly reduced the time to relapse of the disease.[38]

6 | CONCLUSIONS

The majority of available studies on low concentration urea deal with xerosis associated with ichthyosis, atopic dermatitis and psoriasis, or unrelated to specific skin diseases, all showing to be effective. A few

studies also demonstrate that low urea at this concentration is also effective in the treatment of xerosis of the feet in diabetic patients and in tinea pedis in combination with topical antifungals, and for the prevention of relapses of hand eczema and sorafenib-induced hand-foot skin reactions.

Generally, low concentration urea products are well-tolerated (especially if ≤5%) and suited to the treatment of large skin areas, once or twice daily, even for a long period of time. Stinging and burning sensation is rare and transient, while there are no reports of sensitisation despite its widespread use.[39] Finally, the possibility in some disorders of using urea in co-administration with other drugs in order to enhance their penetration/efficacy could represent an interesting approach.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

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