



SUPPLEMENT ARTICLE

DERMATOLOGY

Clinical evidences of urea at medium concentration

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Abstract

Urea-based topical compounds at medium concentrations (15%-30%) represent useful dermatological agents for their humectant and keratolytic effects by enhancing stratum corneum hydration and by loosening epidermal keratin, respectively. The aim of this paper is to review the clinical evidences of the use of 15%-30% urea as single topical agent. Although limited evidence supports the use of these concentrations of urea in skin disorders characterised by xerosis and hyperkeratosis, in clinical practice they are largely used especially in xerosis of limited skin areas, in which the side effects are tolerable, or hyperkeratosis involving large or more sensitive (eg, face, genital region, etc) areas, in which higher concentration may be irritant. In addition, urea at medium concentrations is used in combination with other substances including topical antifungals as penetration enhancer.

1 | INTRODUCTION

Urea-based topical compounds at medium concentration (15%-30%) represent useful dermatological agents for their humectant and keratolytic effects by enhancing stratum corneum (SC) hydration and by loosening epidermal keratin, respectively.¹⁻³ In order to assess the currently available scientific research on the use of 15%-30% urea-based compounds, we conducted a review within the PubMed database using the following keywords: urea[Mesh] AND skin[Mesh] OR moisturising[Mesh] OR keratolytic[Mesh]. All studies identified as relevant, including controlled or uncontrolled clinical trials (CTs), case series, case reports or reviews published in the English literature and having topical 15%-30% urea as single experimental agent were considered. In addition, pertinent references not identified by search engines and retrieved from articles/books were also considered. A brief summary of our results on the use of 15%-30% urea-based compounds in healthy skin and in some dermatological disorders characterised by xerosis and hyperkeratosis is provided. The evidence on the use of urea at medium concentrations in trials/case series ≥ 5 subjects is summarised in Table 1.

2 | HEALTHY SKIN

Some studies conducted on healthy skin have demonstrated the efficacy of topical formulations of urea at medium concentration in

enhancing epidermal barrier function. In particular, an in vivo experimental study on five healthy subjects has demonstrated that after 20% urea-based cream application on the right and the left heels, significant changes of water content (evaluated by diffuse-reflectance near-infrared spectroscopy) was observed in the SC after 1, 2 and 4 hours.⁴ A placebo-controlled, double-blind study on 21 healthy subjects has showed that a 20% urea-based cream, applied once daily on the arms and buttocks for 4 weeks, was able to improve SC hydration by a significant reduction of transepidermal water loss (TEWL) levels from baseline (mean from 10.0 ± 0.9 to 6.9 ± 0.5) evaluated by evaporimeter.⁵ In addition, in the same study, a significant enhancement of expression of some markers for epidermal antimicrobial defence, such as transglutaminase-1, involucrin, loricrin, filaggrin, human cathelicidin LL-37 and β -defensin-2, was found.⁵ Finally, SC penetration of 20% urea was evaluated on the volar forearm skin of six healthy subjects showing, after 15 minutes, a better diffusion of the cream compared with the equivalent solid form, as measured by Raman spectroscopy.⁶

3 | XEROSIS

Xerosis or dry skin is a common skin condition clinically characterised by rough, scaly and often itchy skin. It is mainly caused by a reduction in natural moisturisers factor (NMF), ceramides and/or

TABLE 1 Evidences on the use of urea at medium concentrations (trials/case series ≥ 5 subjects)

Author(s)	Condition	Study design	Urea concentration/formulation	Treatment schedule	Assessment	Outcome
Egawa ⁴	Healthy skin	Open label (n = 5)	20% cream	One application	Instrumental (water content in SC by diffuse-reflectance near-infrared spectroscopy)	Marked changes of water content in the SC
Grether-Beck et al ⁵	Healthy skin	Double-blinded placebo-controlled (n = 21)	10%-20% cream	Once daily for 4 wk	Instrumental (TEWL by evaporimeter and PCR and immunohistochemistry by biopsy)	Significant reduction of TEWL by 20% urea and significant expression of antimicrobial peptide expression by 10%-20% urea
Egawa et al ⁶	Healthy skin	Open label (n = 6)	20% cream and solid form	One application	Instrumental (water content by Raman spectroscopy)	Better diffusion in the SC of 20% urea-cream compared to the equivalent solid form
Banerjee et al ⁸	Palmoplantar keratoderma; pityriasis alba; follicular keratosis; ichthyosiform dermatoses	Open label (n = 49)	20% lotion	Twice daily for 8 wk	Clinical (IGA score)	Moderate improvement of skin hydration in 50,8% of cases, and marked in 12%
Rosado et al ⁹	Severe xerosis	Randomised controlled (n = 12)	15% cream	Twice daily for 2 wk	Instrumental (TEWL by tewameter)	Statistical improvement of TEWL in the treated site compared to untreated
Nash ¹¹	Plantar xeroderma	Randomised (n = 75)	20% cream	Once or twice daily for 28 wk	Clinical (xerosis severity grade)	Significant clinical improvement of xerosis
Baird ¹²	Foot anhidrosis related to diabetes	Open label (n = 30)	10%-20% cream	Once daily for 6 wk	Instrumental (skin hydration by measuring the skin's electrical resistance)	Significant greater increase in skin hydration with 20% cream compared to 10%
Dikes ¹³	Plantar dryness	Open label, compared (two treatment regimens) (n = 22)	25% cream	Once (regimen A) and twice daily (regimen B)	Clinical (xerosis severity by photography) and Instrumental (skin hydration by corneometer)	Significant decrease in the clinical scores and in skin hydration for both regimens
Goldstein et al ¹⁴	Palmar or plantar hyperkeratosis with specific symptoms	Open label (n = 10)	30% foam	Twice daily for 28 d	Clinical (by SRRC scores) and self-assessment of QoL (by Skindx-16 questionnaire)	Significant improvement in clinician's rating of skin condition and in QoL

Abbreviations: IGA, Investigator Global Assessment; PCR, Polymerase Chain Reaction; QoL, Quality of Life; SC, Stratum Corneum; SRRC, Scaling, Roughness, Redness, and Cracks fissures; TEWL, Transepidermal Water Loss.

FIGURE 1 Psoriatic plaques of the abdomen at baseline (A) and after 2 wk of treatment with urea 30% cream (B): complete resolution of the hyperkeratotic component

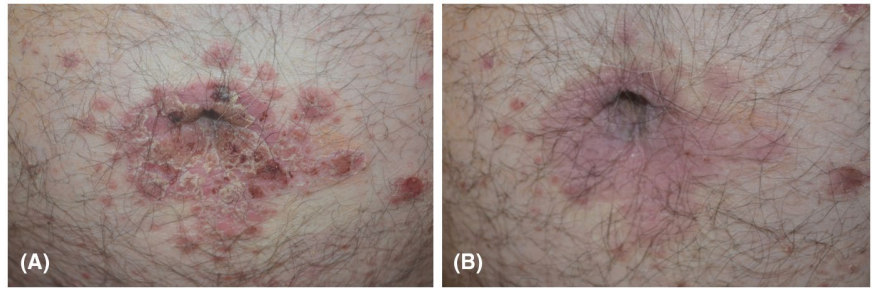
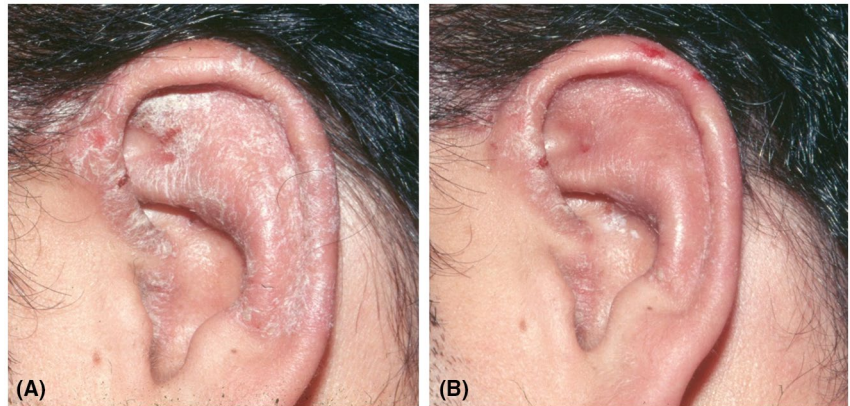


FIGURE 2 Psoriasis of the ear at baseline (A) and after 2 wk of treatment with urea 30% cream (B): complete resolution of hyperkeratosis



aquaporins (AQPs)⁷ and may be associated with some common dermatological disorders, such as palmoplantar keratoderma, pityriasis alba, follicular keratosis, ichthyosiform dermatoses and eczema.

A clinical trial on 27 cases of palmoplantar keratoderma, 13 of pityriasis alba, 10 of follicular keratosis and 9 of ichthyosiform dermatoses, showed that a 20% urea-based lotion, applied twice daily for 8 weeks, was able to induce moderate improvement of skin hydration in 30 cases (50.8%) and marked in 7 (12%), as evaluated by the Investigator Global Score (IGA).⁸ Also, a controlled clinical study on 12 females affected by severe dry skin of the lower legs showed at 2 weeks a statistically significant reduction of the TEWL levels after a twice daily application of a 15% urea cream.⁹

A systematic review has analysed the use of moisturisers for the treatment of foot xerosis.¹⁰ A significant clinical and instrumental improvement using 20%-25% urea creams has been achieved in foot xeroderma related to various conditions such as senile xeroderma, ichthyosis, chronic lichen planus, psoriasis and eczema,¹¹ in bilateral foot anhidrosis related to type 1 and 2 diabetic neuropathy,¹² and in dry plantar skin (Table 1).

4 | HYPERKERATOSIS

Several cutaneous disorders are characterised by dry, cracked and scaling skin correlated to an increase in thickness of the SC because of over-proliferation of keratin-producing cells.¹ In these conditions, urea-based compounds are frequently used for facilitating skin desquamation through the reduction of the cohesion of keratinocytes by breaking hydrogen bonds.¹ Limited evidence supports the use of

urea-based compounds at medium concentration, because generally the keratolytic effect is better obtained by urea at higher concentrations (>30%).

One open-label non-controlled study on 10 patients with hyperkeratosis associated with disabling symptoms, showed that the use of 30% urea-based foam was associated with significant improvement of quality of life evaluated by Skindex-16 questionnaire after 28 day regimen.¹⁴

Also, some authors have showed the effectiveness of 20% urea-based cream/ointment either in the treatment of hyperkeratotic onychomycosis when used for 10 minutes and followed by micro-abrasion prior photodynamic therapy (PDT),¹⁵ as well as in occlusive dressing for 24 hours for nail debridement prior to application of topical antifungal drugs.¹⁶ Finally, some studies on hyperkeratotic type tinea pedis and toenail onychomycosis reported that 20% urea as ointment,^{17,18} cream¹⁹ or nail lacquer²⁰ facilitated a better penetration and efficacy of topical antifungal agents including 2% butenafine hydrochloride,¹⁷⁻¹⁹ 1% fluconazole²⁰ or 2% tolnaftate¹⁸ when used in combination therapy¹⁷⁻¹⁹ or in association (under occlusive dressing technique modality)²⁰ compared with antifungal alone.²¹

5 | CONCLUSIONS

Limited evidence supports the use of urea at medium concentration (15%-30%) in skin diseases characterised by xerosis and hyperkeratosis. This may be explained because in xerosis lower concentrations generally offer good clinical benefits with no significant side

effects,³ and higher concentrations are commonly more effective for hyperkeratosis.

In our clinical practice, urea at medium concentrations has been largely used especially in xerosis of limited skin areas (eg, hands/feet), in which the side effects are tolerable, or hyperkeratosis (eg, psoriasis) involving large or more sensitive (eg, face, genital region, etc) areas, in which higher concentration may be an irritant (Figures 1 and 2). Moreover, we have achieved good results using medium concentration urea in monotherapy to improve xerosis/hyperkeratosis in other conditions such as common warts, actinic keratosis, calluses, epidermal nevi, pityriasis rubra pilaris and Darier's disease, generally with good patients tolerability and compliance.

Finally, urea at medium concentrations used in combination with other keratolytic agents (eg, salicylic acid) for hyperkeratosis¹⁴ or substances including topical steroids and antifungals as penetration enhancer are in selected cases an option worth to consider.

DISCLOSURE

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

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