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History of urea as a dermatological agent in clinical practice

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Abstract

Urea, also known as carbamide, is a polar, hygroscopic molecule produced by the human body that was first discovered in urine in 1773 by the French chemist Hilaire Rouelle and was artificially synthesised from inorganic precursors in 1828 by the German chemist Friedrich Wöhler. The importance of urea in dermatology is twofold: it primarily has a physiological key role for the maintenance of skin hydration, and it secondarily has been used for more than a century in different topical preparation and concentration in various skin conditions. One of the first uses of urea was the topical treatment of wounds because of its antibacterial and proteolytic properties. Since the second part of the 20th century, urea became one of the most common moisturisers and keratolytic agents, useful for the treatment of xerosis, atopic dermatitis, ichthyosis and psoriasis.

Urea (chemical formula: CH4N2O), also known as carbamide, is a polar, hygroscopic molecule[1] produced by the human body that was first discovered in urine in 1773 by the French chemist Hilaire Rouelle. Physiologically, urea plays an important role in the metabolism and excretion of nitrogen-containing products in urine.

The importance of urea in dermatology is twofold: (a) it has a physiological key role for the maintenance of skin hydration being part of the complex mixture of the Natural Moisturising Factor (NMF) of the epidermis[2]; and (b) it is also a compound that has been used for more than a century in different topical preparation and concentration in various skin conditions.[3]

In Europe, Asia and Africa, the therapeutic use of urine (urotherapy) is an ancient practice. Human urine seems to possess good wound healing activity because of the presence of urea. This practice was also mentioned in the Ebers Papyrus of 1500 BC, one of the oldest surviving documents in Egyptian history.

In 1828, the German chemist Friedrich Wöhler obtained urea by treating silver cyanate with ammonium chloride in a failed attempt to prepare ammonium cyanate. This was the first time that an organic compound was artificially synthesised from inorganic precursors, without the involvement of living organisms. Since then, a substantial and evolving literature has been established describing the therapeutic role of urea in dermatology.[4]

In 1917, Symmers & Kirk highlighted the antibacterial properties of urea suggesting its use in wound care as bacteria suspended in certain solutions of urea seem to completely lose the deoxidising power.[5] The application of urea therapy for wound healing was successively supported by other studies confirming its efficacy.[6,7] In wound debridement, urea reveals also proteolytic properties activity and for this reason urea products can be successfully used in necrotic eschars. When a sharp debridement requiring anaesthesia and chemical debridement with enzymatic proteolytic agents, including papain, fibrinolysin-desoxyribonuclease and collagenase, may be marginally and slowly effective and complicated by increased inflammation and pain, urea-containing products may provide a fast and effective softening of large and small eschars through their strong osmotic effect on the skin.[8] In addition, experimental evidences suggest that urea combined with papain in wound debridement, may act as its activator, stimulating its digestive potency.[9]

The year 1957 represents an important date for urea, as Kligman first reviewed its dermatological uses,[10] focusing his attention in particular on its bacteriostatic and proteolytic properties. He reported that, although in vitro 10% urea-containing solutions may exhibit an antibacterial effect on a variety of microorganisms, in vivo higher concentrations (exceeding 40%) are necessary to be effective in dermatologic disorders. Because of unimpressive results at low concentrations, he suggested instead the combined use with antibiotics with the advantage of increase their absorption. As regards the proteolytic properties, he recommended to use only high urea concentrations in compresses and soaks, discouraging the use of

instilling urine (normal concentration of urea of less than 2%) into wounds, therefore, defying previous ancient practices.[10]

In the second part of the 20th century, the importance of urea in the treatment of wound healing declined as it was overcome by the development of more specific and effective medications, while its use as moisturiser and keratolytic agent became more popular. Several studies were conducted on the application of urea in the treatment of xerosis, atopic dermatitis, ichthyosis, psoriasis and other conditions, where low concentrations were generally used on the face and body as general emollients, whereas higher concentrations for thickened skin areas or nails or where a fast and keratolytic action was needed.[2,11] Another field of growing interest was the association of urea with other active ingredients, such as topical corticosteroids[12,13] and antifungals,[14] in order to enhance their penetration into the skin.

Modern studies are disclosing other unexpected properties of urea. In murine model of atopic dermatitis, urea has been reported to act as regulator of genes that impact keratinocyte differentiation, lipid synthesis and antimicrobial peptide production, leading to enhanced permeability barrier function and likely antimicrobial defence.[15] In addition, in a randomised controlled trial, urea-containing products have also been shown to accelerate barrier repair following surfactant-induced irritation and protect against further irritation with repeated exposure.[16]

Recently, the use in oncology of new target systemic treatments (eg, multikinase inhibitors) resulted in the onset of new dermatologic adverse events, including the hand-foot skin reaction clinically characterised by painful hyperkeratosis. A randomised study on patients with advanced hepatocellular carcinoma treated with sorafenib has demonstrated that urea-based preparations are able to successfully manage and prevent this side effect.[17]

In conclusion, although new ingredients and formulations are continuously marketed, urea still remain one of the most effective and safe molecules in the treatment/prevention of selected skin disorders because of its wide molecular and functional properties associated with low toxicity and side effects.

DISCLOSURE

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

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