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Urea creams in skin conditions: composition and outcomes

David Voegli
PhD BSc RN Lecturer,
Faculty of Health
Sciences, University
of Southampton

The use of urea as a healing agent goes back thousands of years. Urea was the first organic compound to be synthesised in a laboratory from inorganic materials, and urea preparations were used in the late 19th and early 20th century for the topical treatment of infections.¹ Interest in urea as a topical agent to treat dry skin disorders developed over 50 years ago, following the discovery that urea played an important role in moisture regulation, and was a key constituent of natural moisturising factor (NMF).² It was also observed that skin urea levels appeared to be depleted in some dry skin conditions and the logical way forward was to develop urea-containing preparations to replenish epidermal levels and skin hydration. Dry skin is seen in several skin disorders, such as atopic eczema, ichthyosis, and contact dermatitis. The reduction in the water content of the epidermis changes the properties of the skin barrier, favouring the penetration of irritants, as well as reducing the itching threshold and predisposing the skin to infections. This paper outlines the chemical properties of urea and its clinically proven effectiveness in the management of dry skin disorders, when incorporated into emollient formulations.

Chemistry

Urea is an important molecule involved in nitrogen metabolism and transport in humans. It is an end product of protein catabolism, formed in the body by the oxidation of amino acids in the liver, and regulated by the enzyme N-acetylglutamate. Pure urea forms as small white crystals, giving it a powdery appearance. It is highly water-soluble, only slightly soluble in alcohol, and virtually insoluble in other organic solvents, such as chloroform and ether. Due to the relatively low cost of production, urea has become an important raw material in several manufacturing processes, ranging from agricultural fertilisers, plastics and paper, through to pharmaceuticals and cosmetics. Urea crystals are hygroscopic; they attract and hold water molecules from the surrounding environment, making it an ideal ingredient for a skin moisturiser. Hygroscopic substances are fre-

quently used in pharmaceuticals, cosmetics and processed foods to attract water and retain moisture. When used in this context, the term humectant is generally used to describe a substance that absorbs water or helps another substance retain moisture. Substances, that have similar properties to urea and also act as humectants to increase the water content of the stratum corneum (CSC), include glycerin, sorbitol, alpha hydroxy acids, and some complex sugars.

As urea is a fairly simple molecule and highly water-soluble, it is easily incorporated into dermatological preparations. However, urea and urea solutions are relatively unstable and on standing, heating, or exposure to acids or alkalis, urea is hydrolysed to ammonia and carbon dioxide. This instability in water-based formulations led to problems in the development of the original urea creams, producing an unpleasant smell of ammonia, necessitating refrigeration and shortening shelf-lives.³ Decomposition is solved by adding stabilisers, such as sodium lactate, lactic acid, lactones or the use of a water/propylene glycol mix as a solvent. Numerous patents have been filed specifically related to the stabilisation of urea in dermatological and cosmetic products. However, it has been shown that the addition of excipients can influence the moisturising efficacy of urea when Couteau *et al* compared different formulations of an emollient with the same concentration of urea (5%).⁴ Similarly, the keratolytic effects of urea that occur with concentrations greater than 10% are enhanced in the presence of highly occlusive agents, such as petrolatum.

Action of urea on the skin

In normal health, the SC contains approximately 10–20% water and, should the water content fall below 10%, then the clinical signs of xerosis become obvious. This water is divided between the relatively constant amount associated with the hydrophilic parts of the intercellular lipids and keratin fibres in the corneocytes, and that bound to hygroscopic substances found within the skin, which varies according to the relative humidity of the environment.⁵ The hygroscopic substances found within the corneocytes are collectively termed

Table 1. Chemical composition of NMF found in the epidermis (Adapted from Verdier-Sévrain *et al*,2007).⁵

Substance	Composition (%)
Free amino acids	12
Pyrrolidone carboxylic acid (PCA)	12
Lactate	12
Sugars	8.5
Urea	7
Chloride	6
Sodium	5
Potassium	4
Ammonia, uric acid, glucosamine, creatine	1.5
Calcium	1.5
Magnesium	1.5
Phosphate	0.5
Citrate, formate	0.5

NMF, and the increase in intracellular water they promote helps the corneocytes to retain their turgidity and shape, thus maintaining a coherent barrier. The presence of NMF tends to increase the water content of the SC whenever the ambient relative humidity exceeds 40–50%.⁶ NMF is principally derived from the breakdown of the protein filaggrin, and consists of a complex mixture of free amino acids, amino acid derivatives and salts, with urea being a major factor – constituting about 7% (see Table 1).⁵ Thus, urea is able to attract water from two sources; it enhances water absorption from the dermis into the epidermis and, in humid conditions, it can also help to absorb water from the external environment.

Urea is traditionally used in dermatology as part of the management of xerotic conditions such as atopic eczema, ichthyosis, contact dermatitis, psoriasis and as an antipruritic. The main sources of urea in the epidermis are from sweat and the decomposition of arginine by arginase during the keratinisation process.⁷ The unique properties of urea in the skin are mainly due to its ability to break the hydrogen bonds in protein chains and alter their configuration, particularly keratin. At high concentrations (over 10%), it exerts a pronounced keratolytic effect, and has been shown to enhance cutaneous permeability to some substances (such as, steroids), thereby showing a synergistic effect with other topical agents. At concentrations $\leq 10\%$, it favours the bonding of water to the protein chains in the SC, increasing hydration.³ The increase in SC hydration and restoration of the skin barrier reduces the itching sensation (correct?) – making low concentration (5%) urea creams a useful agent in pruritus.

Table 2. Urea-containing emollients listed in the *British National Formulary* (September 2012)⁸

Product	Manufacturer	Form	Urea content (%)	Net price (£)/100g
Aquadrate®	Alliance	Cream	10	4.37
Balneum®	Almirall	Cream	5	4.60
Calmurid®	Galderma	Cream	10	5.70
Dermatonic Heel Balm®	Dermatonic	Cream	25	4.75
E45® Itch Relief Cream	Reckitt Benckiser	Cream	5	3.47
Eucerin® Intensive	Beiersdorf	Cream	10	7.59
Hydromol® Intensive	Alliance	Cream	10	4.37
Nutrplus®	Galderma	Cream	10	4.37
Alphaderm®	Alliance	Cream	10 plus 1 hydrocortisone	7.03
Calmurid HC®	Galderma	Cream	10 plus 1 hydrocortisone	8.76
Hydromol® HC Intensive	Alliance	Cream	10 plus 1 hydrocortisone	7.03

Dermatological preparations

A number of topical urea preparations are available in the UK. Most are available over the counter (see Table 2).⁸ For general emollient uses, the urea content ranges from 5 to 10%, although preparations with a urea concentration ranging from 5 to 22% are marketed elsewhere, and are potentially available via the internet. A lower concentration is generally used on the face and body, whereas a higher concentration may be applied to thickened skin areas or where a quicker response is desired. An improvement in skin hydration, as measured by corneometry, has been reported in as little as four hours following application of one dose of a 10% urea-containing emollient, and can last for over six hours. Similar results were obtained with a 5% cream, although the hydrating effects started to decrease after four hours.⁹ In podiatry, 25% urea creams are used to treat and remove dry skin, particularly on the heels and feet, and urea-containing products have proved useful in the treatment of anhidrosis in the diabetic foot.¹⁰ Urea solutions of 40% can be used to avulse toenails, or enhance the penetration of antifungal agents into the nail.

Numerous clinical evaluations of urea-containing products across a range of dermatological diseases have been performed over the years and, although now rather dated, most have demonstrated a significant improvement in skin condition following the application of urea across a range of concentrations.³ They have also been shown to accelerate barrier repair following surfactant-induced irritation and protect against further irritation with repeated exposure.¹¹ A more recent application of urea-based creams has been in the prevention and management of the skin reaction

seen in oncology patients being treated with multikinase inhibitors (sorafenib and sunitinib). In this indication, urea cream prophylactic use proved effective in trials in preventing or delaying the onset of skin problems.¹² Urea creams have been extensively studied in the management of atopic eczema, and it is here that they have really found their niche. Although the moisturising and skin barrier restoring effects of urea are well documented the correlation between efficacy and concentration has not been extensively studied. More recent attempts to explore this have compared low urea concentrations (3% and 5%) with a higher concentration (10%). Sant'Anna Addor *et al*⁹ confirmed a significant increase in moisturisation with both a 5% and 10% urea formulation, although the 10% concentration achieved a faster response and lasted longer. Unfortunately, the 10% formulation was associated with increased reports of irritation. A similar study by Bissonnette *et al*¹³ in atopic eczema, showed a significant improvement in skin condition following application of both concentrations of urea, as measured using the Scoring Atopic Dermatitis tool.¹⁴ However, they also reported that some volunteers experienced irritation with the 10% urea concentration, and that, overall, volunteers expressed a preference for the 5% formulation.

Generally, urea-containing emollients are well suited to the care of large areas of skin, even over long periods. It is recommended that such emollients are used once or twice a day as an add-on therapy to the regular emollient regimen, which should form part of 'complete emollient therapy' – that is, using a combination of cream, ointment, bath oil and emollient soap substitute.¹⁵

Adverse effects of urea creams

Urea creams are generally regarded as having few adverse effects, and there are no reports of sensitisation to urea, despite its widespread use. Indeed, a recent toxicology report by the US Environmental Protection Agency confirms it as having a good safety profile.¹⁶ Some patients have reported skin irritation from urea preparations, such as redness, stinging, and a burning sensation, as already mentioned. In most cases, these sensations are transient and relate to urea concentration, and were more of a problem with the early formulations of urea-containing emollients.¹⁷ Newer formulations appear to be well tolerated and suitable, even for sensitive skin, with the standard concentration being 5% urea. The application of any topical agent can cause stinging, but this is not necessarily sensitisation. However, the risk of sensitisation to excipients still exists, as with any emollient. Although this may occur, in practice it is not a significant

problem. Fewer than 20% of patients report adverse reactions to their emollient, compared with more than 55% of those using aqueous cream.¹⁸

Summary

Urea has a long history in the treatment of dry skin conditions, and has proved to be a safe, reliable agent. Urea-containing creams provide a useful adjuvant emollient in the treatment of atopic eczema, ichthyosis, psoriasis and the diabetic foot. At low concentrations, urea is able to change the structure of proteins, particularly keratin, in the SC, increasing water-binding capacity and hydration, while at high concentrations it exhibits a proteolytic action, dissolving keratin. Overall, urea creams are also able to affect epidermal lipid synthesis and promote skin barrier repair ■

Declaration of interest

The author declares that there is no conflict of interest in the writing of this paper.

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Key points

- Urea-containing formulations are a useful adjuvant emollient in dry skin conditions and pruritis.
- Urea creams have been shown to have a significant positive effect on skin hydration and barrier function.
- A range of concentrations of urea creams is available, although a low-concentration 5% preparation is recommended for general use.
- Although suitable for sensitive skin, application of urea creams can cause transient stinging or burning.