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# Urea in the Treatment of Dry Skin

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**Urea is a unique physiological substance. It has frequently been used in dermatological therapy for more than 20 years. The relevant properties of urea with regard to its use in dermatological preparations are discussed in this brief review. Urea's natural presence in the horny layer, its water solubility, dipolar character and relation to concentrated solutions of electrolytes, are highlighted. The clinical use of urea creams is discussed with respect to indications, side-effects and combinations with other substances.**

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Urea has been used extensively during the last two decades in the treatment of dry skin, both clinically and in cosmetic products. Its popularity is probably due to its effectiveness, good cosmetic properties and its being non-toxic and non-allergenic.

Urea is in many respects an interesting substance, not least for being the first organic compound that was synthesized by man in a laboratory (Wöhler, 1828). Urea is also a major constituent of the water-soluble fraction of the normal horny layer and thus a part of the natural moisturizing factor. In the following I shall discuss some of the properties of urea that are of interest for its use in dermatology but also touch upon its clinical use.

*Urea is very soluble in water* but practically insoluble in lipids and lipid solvents. In a cream base urea is thus present only in the water phase. In the horny layer it is probably present intracellularly within the fibrous keratin and not in the lipid environment of the intercellular space.

Urea's high solubility in water gives saturated solutions a low water vapour pressure. This means that the solutions take up water from the atmosphere when the relative humidity is high.

Urea's solubility is not so high, however, as to make it hygroscopic under normal conditions.

*Urea is an end product in the catabolism of proteins.* It does not contain much energy and cannot be utilized as an energy source by most microorganisms. Contrary to free amino acids, another major constitutent of the natural moisturizing factor of the horny layer, urea does not function as a nutrient for pathogenic microorganisms.

In high concentrations, *urea is a hydrogen bond breaker.* It can therefore disperse proteins and gain access to the interior of fibrous protein material such as epidermal keratin. It does not change the primary structure of protein – only their configuration. It has been used to extract epidermal keratin for biochemical studies.

*Urea has a high dipole moment* that might be of importance for the ionic activity of very concentrated salt solutions. Urea's presence in high concentrations only slightly diminishes the solubility of electrolytes in water, giving the solution a water vapour pressure that is lower than that of a saturated salt solution without urea. This might possibly be the explanation for the synergistic effect with regard to water binding found between urea and sodium chloride (1). Together, urea and sodium chloride have a higher water binding effect than can be obtained by either of the two substances alone.

*Urea binds water in the horny layer.* In 1952 Blank (2) showed that the horny layer needs water – and not lipids – to become soft and pliable. Some years later (3) it was shown that the horny layer contains large amounts of water-soluble, low molecular weight substances that have the ability to bind water. In 1968 I showed that, when added to scales from psoriatic and ichthyotic patients, urea strongly increased the water binding capacity (4). The relative humidity at which the urea-treated scales take up water is higher than we usually have in the atmosphere. However, the very thin horny layer rests on the wet surface of the granular layer. It takes water from below and evaporates water into the environment, but keeps enough water to remain soft and pliable. Its not in equilibrium, but rather in a steady state of flux of water outward through the horny layer.

*Urea has an antipruritic effect* that can be demonstrated experimentally in a controlled double-blind study (5). This effect is probably due to its slight anesthetic effect. In diseases such as atopic eczema this property may be of importance.

*Urea has been shown to be clinically effective.* It could also be shown that 10% urea in a cream base, applied daily, greatly improved the skin in ichthyotic patients (4). A large number of studies, both in vitro and clinically, have confirmed the beneficial effect of urea creams (7,8).

*Urea creams are useful for all degrees of dry skin.* It was soon evident that urea creams were also useful for other with dry skin conditions, even dry skin without any clinical sign of disease. This potent remedy for ichthyosis vulgaris could also be used on apparently normal looking skin without causing any side-effect. There seems to be a self-regulating effect of urea creams. If the skin is very dry and scaly, a large amount of the cream is taken up by the horny layer. But if the horny layer is thin and has a normal water content, very little of the cream is actually taken up when the cream is applied in a normal way. It does not seem possible to obtain an excess hydration of the horny layer with urea creams. A temporary high water content of the urea treated horny layer increases the water vapour pressure. Consequently, the evaporation of water normalizes the water content.

*Formulations of urea preparations for dry skin.* It was clear that the content of urea in such a preparation has to be high in

order to be effective. It was also clear that a pure solution of urea in water would leave a white urea powder on the skin and very little effect would be achieved. By adding lactic acid to the solution, urea penetrated effectively into the horny layer. Lactic acid also preserved the preparation, rendering other preservatives unnecessary. Urea could also be added to a cream base, though this had to be stable in order to take as much as 10% of the urea into the water phase.

The first commercial urea containing preparation for dry skin therefore contained both urea and lactic acid. The first medical urea product was Calmuril, followed by a cosmetic product called HTH in Sweden (HDS Helps Dry Skin).

Some years later van Scott (8) showed that alpha hydroxy acids, one of which is lactic acid, have a keratolytic effect in ichthyosis vulgaris.

In 1974, I found that a combination of urea and sodium chloride gave a still better water-binding effect (1). The two substances have in this respect a synergistic effect. As was mentioned above, this is probably due to urea being a strong dipole, making it possible to act together with sodium and chloride ions to reduce the water vapour pressure.

*Does urea have a keratolytic effect?* It depends on what we mean by keratolytic. In certain conditions, such as psoriasis and ichthyosis, the building up of thick scales seems to be due to the dryness of the horny layer. The scales can be removed by immersing the skin in water or occluding the skin with a material impermeable to water. In keratodermia palmoplantaris, the horny layer is not dry. The defect might be in the enzymes that can break down the desmosomal proteins. Urea may be regarded as keratolytic in the former sense, but not in the latter. To my knowledge, only retinoids are effective keratolytically, by altering epidermis metabolically.

*Clinical use of urea preparations.* The diagnosis that initiated the use of urea creams, ichthyosis vulgaris, has remained the condition in which the effectiveness of topical urea treatment can best be demonstrated. Apart from the original report (4) a number of studies have demonstrated the efficacy of this treatment (7,8).

Another disease where urea creams are of great value is hand eczema, especially the irritative and atopic type. Regular use of urea creams after each time the patient has been in contact with water may have a good preventive effect. A common use of urea creams is maintenance treatment of different types of eczema after a short period of topical treatment with corticosteroids.

Dry and xerotic skin of unspecified etiology also responds very well to treatment with urea cream.

In my experience urea creams are suitable as emollients for psoriatic patients who either do not need to be completely healed or are using some other active principle, such as UVB irradiation, dithranol, or methotrexate.

*The combination of urea and steroids in a cream base* has been found very useful, especially in the treatment of different types of eczema. Atopic eczema responds well to this treatment. This treatment has also been used for hand eczema.

*Does urea increase the penetration of steroids or other compounds?* Several studies have been published on this question. Some have shown an increased penetration (9), while others have found no such effect (10). I find it unlikely that urea has a significant effect on the epidermal barrier. The potentiation of the effect of corticosteroids by urea in a cream base is probably because urea restores the barrier by preventing dry cracking of the horny layer and thereby eliminates one irritative factor.

I have the impression that a fat ointment, such as vaseline, macerates the horny layer and thereby increases the penetration. I have often found in psoriatic and eczema patients who have used vaseline and then tried a urea cream, that there will be a stinging sensation that cannot be reproduced after a few days' use of the cream. My interpretation is that vaseline has destroyed the barrier, so that the hypertonic water phase of the urea cream causes the stinging. The barrier is then soon repaired after a short time with urea cream treatment. In most conditions I find it likely that urea improves the barrier function rather than destroying it.

*Side-effects of the use of urea creams.* No long-term side-effects have been found. To my knowledge, there is no report published of contact allergy. In spite of common use for many years, no epidermal or dermal atrophy has been reported.

The problem is the stinging effect, especially in children with atopic eczema. For this reason I do not recommend the use of urea cream in children under the age of five. If adults are informed about a possible stinging on eroded or fissured skin, there is usually no problem.

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