

BIOLOGICAL FUNCTIONS AND THERAPEUTIC PROPERTIES OF UREA

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Synopsis

Although urea is known for about 50 years, its use as a topical drug or as an adjunct is obtaining more and more attention in topical dermatotherapy. Urea is absolutely non-toxic, undesirable actions occur only, if skin state and concentration of urea are on a disbalance. Urea proved to be a most valuable substance for restoring hydration in dry skin and in eczemas due to skin dryness. Therefore, urea ranks among the standards in atopy, for the treatment of eczema as well as for the interval care.

Riassunto

Sebbene si conosca l'urea già da circa 50 anni, il suo uso come farmaco o cosmetico topico sta ottenendo sempre più attenzione nella dermatoterapia topica.

L'urea è assolutamente atossica e si possono verificare effetti indesiderati solo nel caso in cui le condizioni della pelle e la concentrazione di urea siano sbilanciate.

L'urea ha provato di essere una sostanza di grande valore per il ripristino dell'idratazione nella cute secca e negli eczemi causati dalla cute secca. L'urea si colloca quindi tra le scelte standard nei casi di atopia, per il trattamento degli eczema e per le terapie di intervallo.

INTRODUCTION

Urea (carbamide), the diamide of carbonic acid, is a naturally occurring degradation product of various proteins in man. Up to 30 g were produced daily. Urea is found in all organs and body liquids. On the skin surface, urea is an important component of the natural moisturizing factor contained in the hydrolipid emulsion.

About 50 years back, urea was recommended for the topical treatment of hand eczema but only 30 years back, the first experimental data were collected on its biochemical and pharmacological activities. The moisturizing capacity of urea in the stratum corneum, especially in xerotic states, was discovered. In 1988, a symposium was held in Salzburg, Austria, the proceedings of which contain all the information available on the various actions of urea in dermatology and cosmetology (1). The more recent publications are compiled in a review article published 1993 (2).

Today, urea belongs to the standard substances used in dermatological therapy and skin care.

TOXICITY

Urea lacks any systemic toxicity. Urea formerly was used as a diuretic drug; doses up to 1.0 g/kg bodyweight were given intravenously, without any undesirable action.

Therefore, following absorption from external preparations, no toxic effects of urea can be found.

The tolerance of urea depends on the state of the skin and on the concentration of urea. The vehicle applied may influence the tolerance, too. On healthy skin, urea may be used in concentrations up to 20%. Most products, however, contain 5-10% of urea, only, as irritating effects on slightly damaged skin should be avoided. Such effects might develop as a consequence of osmotic activity.

BIOCHEMICAL FUNCTIONS OF UREA ON THE SKIN

Urea is an important component of the natural moisturizing factor of the stratum corneum. Water is bound by an inclusion in the crystal structure of urea and only slowly liberated. Urea stems from the sweat and from the process of keratinization. The natural moisturizing factor consists of various ions (24%), pyrrolidone carboxylic acid (12%), various other carboxylic acids (50%), amines and amides (17%) and urea (7%). One should not underestimate the amount of natural moisturizing factors in the stratum corneum which make up about 25% of the dry weight of the total horny layer.

Stratum corneum of healthy skin contains about 40 M urea per 10 M amino acids which corresponds to about 28 $\mu\text{g}/2.5 \text{ cm}^2$ (2). In dry skin, urea content is significantly lower (50% in some instances, only). Clinically normal skin of atopic individuals contains only 30% urea compared to normal values. In clinically diseased skin (atopic eczema), urea content is lowered to 20% of normal values (Fig. 1, 2).

From these data the conclusion may be reached that urea is one of the most important components of the natural moisturizing factor of human skin.

MOISTURIZING ACTIVITY OF UREA

Urea exerts a wide range of pharmacological activities when applied on the skin:

- moisturizing activity,
- desquamating action (lysis of cementing substance),
- antimicrobial action (uptake of water interferes with the growth requirements of microorganisms).

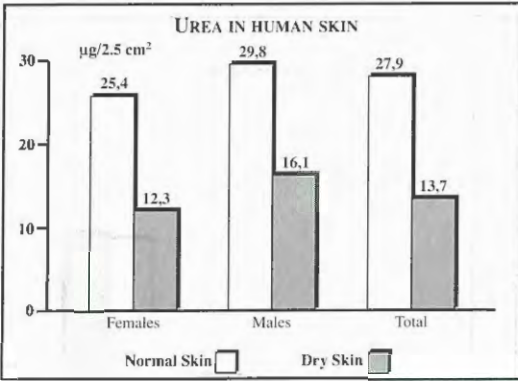


Fig. 1

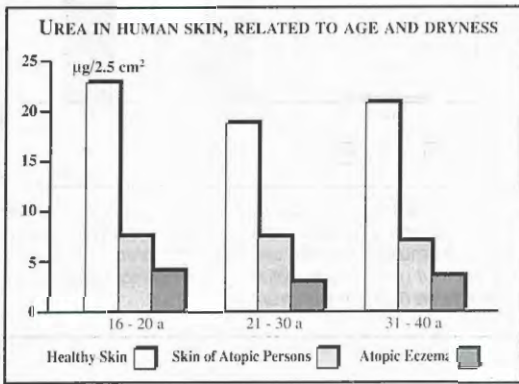


Fig. 2

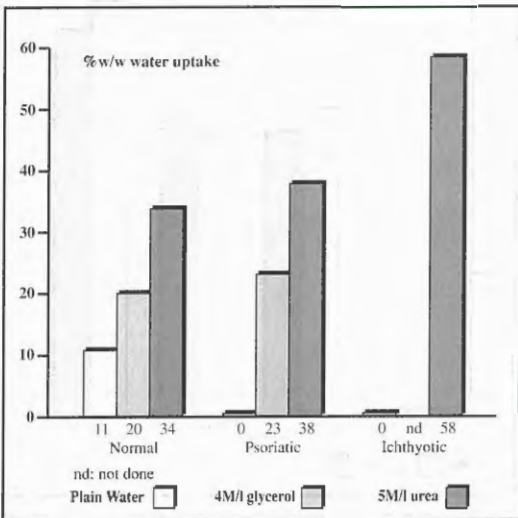


Fig. 3: Water uptake of normal, psoriatic, and ichthyotic stratum corneum following immersion in various solutions (Swanbeck, from 3).

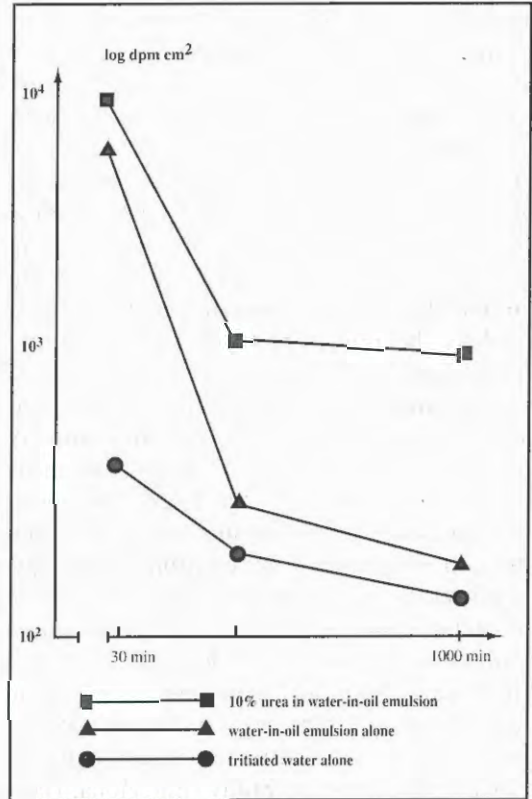


Fig. 4: The influence of urea on the water binding capacity of human stratum corneum (Wohlrab from 3).

- "antiinflammatory" action (antiproliferative, antiedematous, antipruritic).
- enzyme inhibiting action (mostly against proteases) and
- keratolytic action (true keratinolysis occurs under the influence of urea in a concentration of 40%).

The most important (and therapeutically most widely used) action of urea is its moisturizing capacity. By immersing stratum corneum from dry skin (psoriatic, ichthyotic) in 5 M urea/l, the uptake of water could be significantly increased. In these experiments, urea showed definitely higher activity than glycerol, a humectant which is widely used in cosmetic products. In another series of experiments, tritiated water was applied on the skin surface in the form of a water-in-oil

emulsion with 10% urea. The water retention, judged by how long tritiated water could be detected and in which amount, was significantly higher than in the controls with the vehicle alone. (Fig.4).

The application of urea containing emulsions decreases skin roughness due to the moisturizing action of urea; maybe, the desquamating action of urea contributes to this effect. In atopic skin, this decrease in roughness, judged by the replica method, was especially pronounced. (Fig. 5, 6).

A vast number of experiments has been conducted to ascertain the moisturizing property of urea (figures 3, 4, 5, 6). Various methods have been used to probe this effect: corneometry, measurement of conductivity, evaporimetry and profilometry. By electron microscopy, a loosening of the layers within the stratum corneum could be demonstrated, indicating a moisturizing effect (2). Cf. Fig. 7, 8, 9.

In diseased skin, too, experimental investigations have been performed to demonstrate the moisturizing (and antieczematous) action of urea. In the European Study (Barcelona, Hamburg, Vienna) a statistically significant increase in moisture and a statistically significant decrease in TEWL occurred following a four week treatment of atopic eczema with a preparation containing 10% urea (4). Cf. Fig. 10.

KERATOLYTIC AND DESQUAMATING PROPERTIES OF UREA

In concentrations up to 20%, urea exerts a concentration-depending desquamating action on the stratum corneum. By this effect, skin penetration is facilitated. Cf. Fig. 10, 11.

In a 40% concentration, urea has been shown to exert true keratolytic properties. Nail plates in fungal diseases may thus be dissolved.

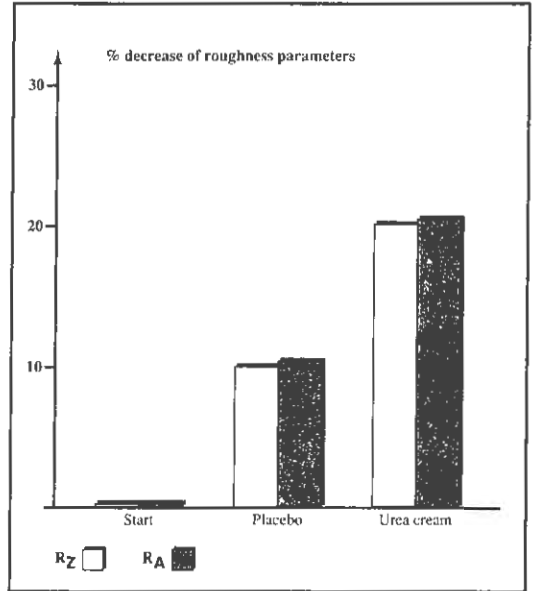


Fig. 5: Decrease of skin roughness parameters RZ and RA 60 min. after the application of a silicone-containing water-in-oil emulsion with 5% urea as compared to the vehicle without urea. Mean values of ten normal individuals were given (Puschmann from 3).

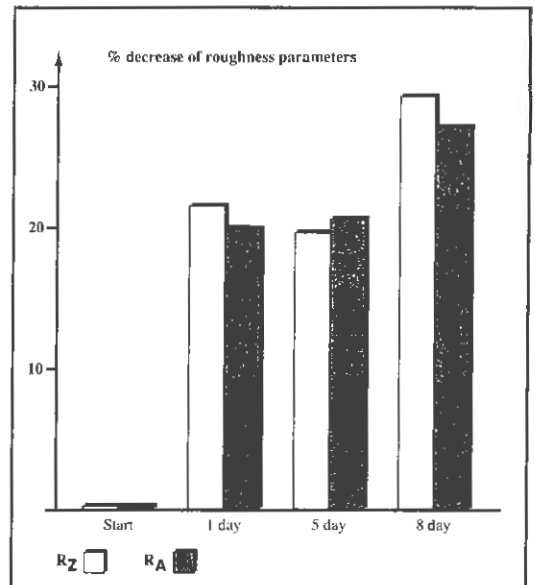


Fig. 6: Decrease of skin roughness parameters RZ and RA following the use of a silicone-containing water-in-oil emulsion with 5% urea. Mean values of 9 atopic individuals were given (Puschmann, from 3).

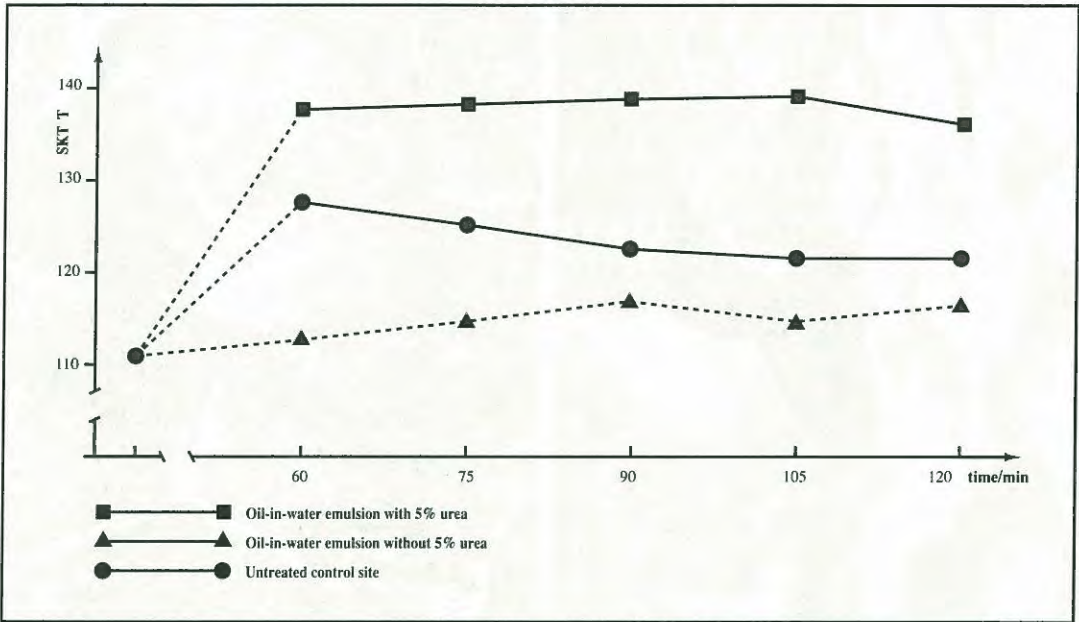


Fig. 7: Skin moisture after application of a silicone-containing oil-in-water emulsion with and without 5% urea, measurement by determination of the dielectric constant. Mean values of 35 healthy individuals were given. (Puschmann, from 3).

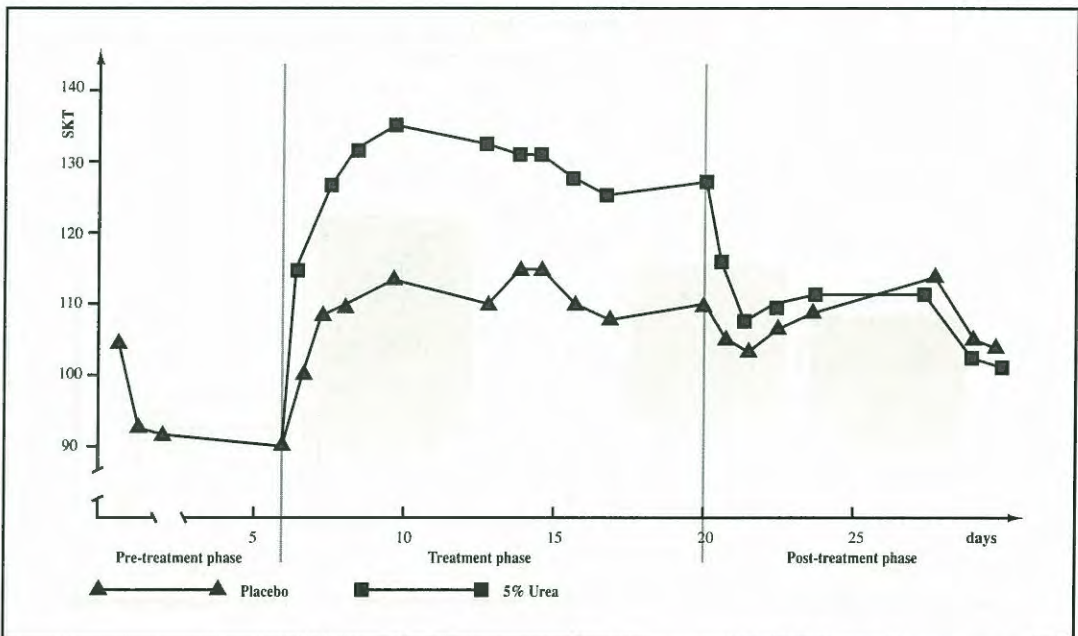


Fig. 8: Skin moisture following the application of a silicone-containing oil-in-water emulsion with and without 5% urea for two weeks. Mean values of 6 healthy individuals were given (Puschmann, from 3).

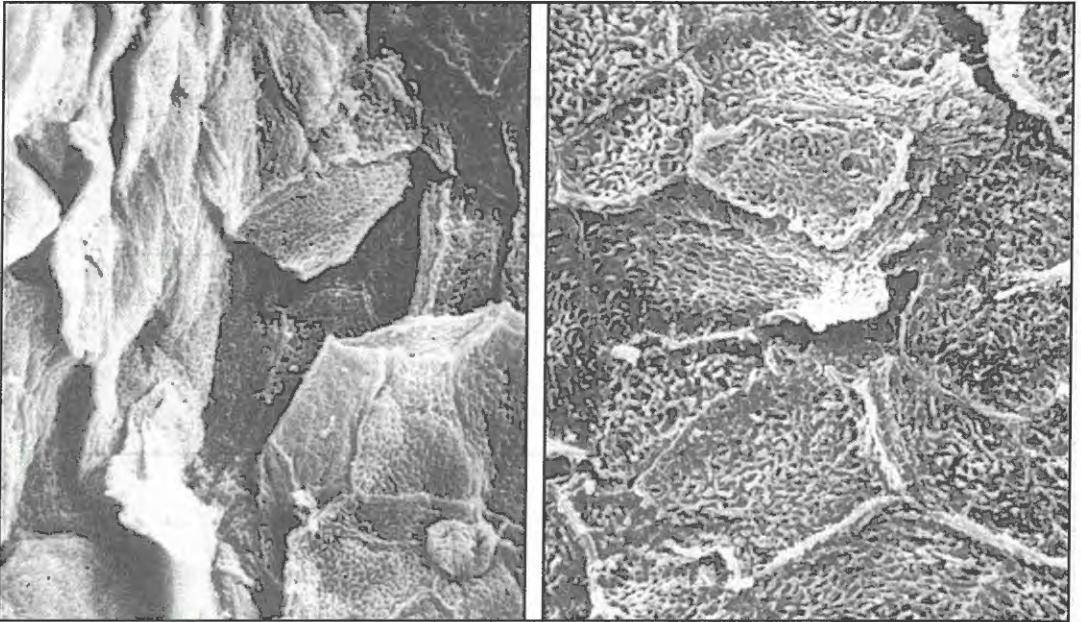


Fig. 9: Hyperkeratotic skin in chronic eczema before and after the application of urea 10% + salicylic acid 5% for 10 days. REM, material from biopsies, magnification 2.500 x. From 2, with the permission of the authors Plugshaupt and Früh.

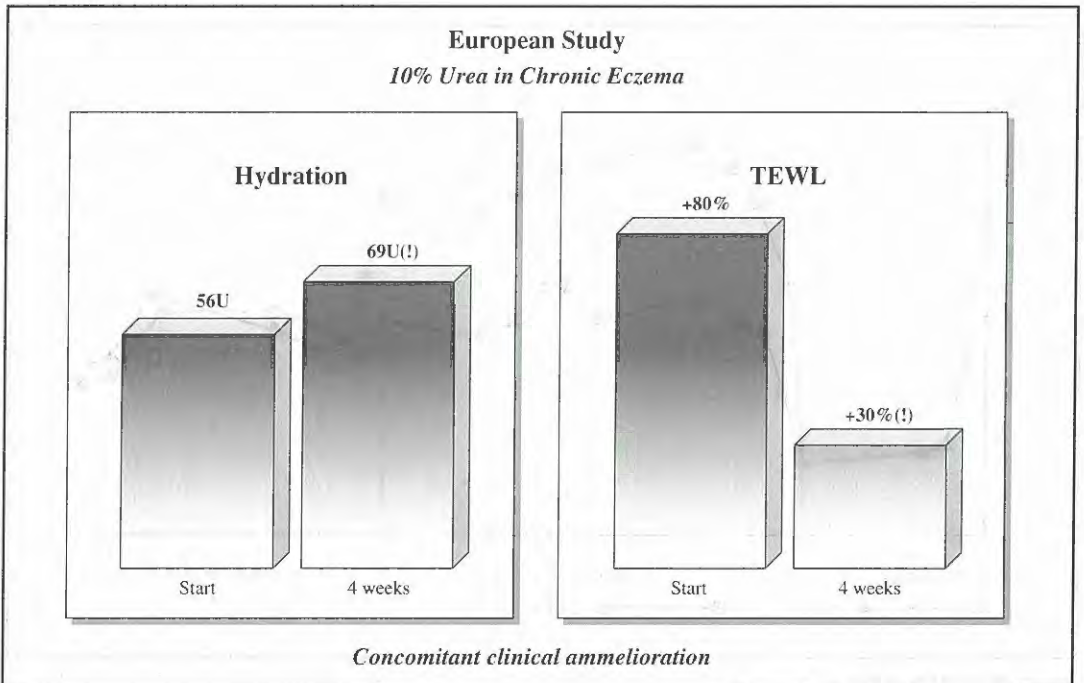


Fig. 10

ANTIINFLAMMATORY ACTIONS OF UREA

An antiproliferative effect of urea has been demonstrated in states of accelerated cellular turnover (e.g. psoriasis vulgaris) but no atrophogenic effect in normal skin could be observed.

The antiedematous action of urea is connected with its diuretic activity. In states of lymphostasis, a dramatic response can be evoked by topical applications of 10% urea.

The antipruritic activity of urea mainly is due to its moisturizing capacity. On the other hand, a directed influence of urea on those enzymatic activities which provoke itch could be demonstrated.

ANTIMICROBIAL ACTIVITY OF UREA

By its strong water binding capacity, urea inhibits the growth of microorganisms. Therefore, urea may be regarded as a preservative-saving substance.

UREA COMBINED WITH OTHER DRUGS

Via three mechanisms, urea increases the pharmacological activities of other simultaneously applied drugs:

- via its moisturizing capacity (increased absorption),
- via its desquamating properties (increased absorption) and
- via the formation of hydrophilic adducts (increased release from the preparation and increased uptake by the skin).

Lastly, synergistic effects much be mentioned between urea and some topically applied drugs with antiinflammatory or keratolytic action. An example is shown in Fig.9.

USES OF UREA IN DERMATOLOGY

Urea alone

Dry skin, old skin, photodamaged skin.
Atopic skin, (therapy and interval skin care).
Psoriasis vulgaris and other scaly dermatoses.
Ichthyosis and ichthyosiform skin conditions,
hyperkeratoses, keratoses.
Onycholysis (40%)

Urea in combinations

With glucocorticoids (hydrocortisone, halcinonid): atopic eczema, chronic dry eczema, Psoriasis vulgaris, all old, hyperkeratotic, scaly, resistant inflammatory skin lesions. (5-10% urea, 0,1-1% steroid).

With anthralin (17% urea + 0,5-2% anthralin): Psoriasis vulgaris, prolonged applications or short contact therapy.

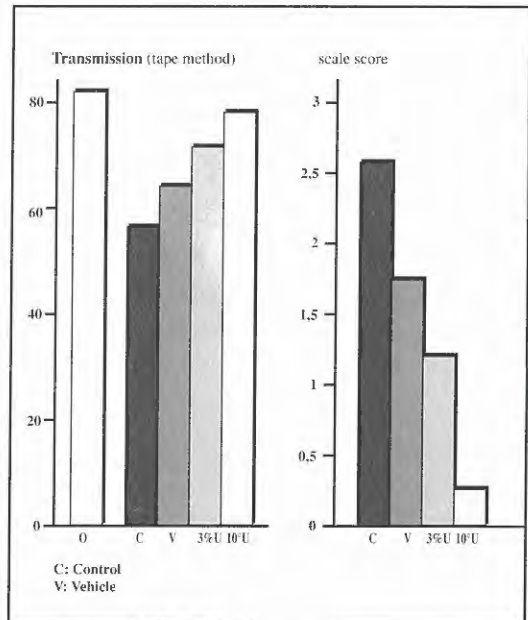


Fig. 11 - Desquamating action of urea

With polydocanol (5% urea + 3% polydocanol): atopic eczema, treatment and interval skin care.

With tretinoin (10% urea + 0,03% tretinoin): non-inflammatory, non-erythrodermic ichthyosis.

With salicylic acid (10% urea + 5% salicylic acid): stubborn hyperkeratosis, corns, eventually warts.

With bifonazole (40% urea + 1% bifonazole): onychomycosis.

Among the combinations of urea with other drugs, the preparations containing urea and a glucocorticoid have found widest application. Urea increases the bioavailability of the steroid ("hydrocortisone develops into triamcinolone") but does not alter the incidence and severeness of undesirable effects.

REFERENCES

1. Raab, W. (Editor) (1989), Harnstoff in der Dermatologie, *Hautarzt* **40**, Suppl. IX.
2. Raab, W. (1993), Harnstoff in der Dermatologie, *TW Dermatologie* **23**: 257-269.
3. Raab, W. (1990), Use of urea in cosmetology, *Cosmet. Toiletr.* **1054**: 97-102.
4. Vilaplana, J. et al. (1994), Internationale, multizentrische Prüfung der Wirksamkeit und Verträglichkeit der externen Therapie chronischer Ekzeme mit einem 10% igen Harnstoffpräparat, *Akt. Dermat.* **20**: 227-231.

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