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USE AND EFFICACY OF UREA IN DERMATOLOGICAL PREPARATIONS

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Synopsis

The basis of the effects of urea on the human skin is its penetration kinetics into different skin layers. A strong vehicle dependence can be estabilished. Therefore wide differences are found in the duration and intensity of increased water-binding capacity after application of different urea containing emulsions. For therapy to increase the hydration and water-binding capacity in the horny layer of diseased skin preparations with 10% urea are more suitable than those containing 2% or 5% urea. For cosmetic preparations, the higher concentrations of urea are inappropriate, lower ones are sufficient. By altering the functional structure of the horny layer and increasing of drug liberation from ointment bases, urea is one of the most effective penetration promoters. An increased penetration rate of some corticosteroids, dithranol and other drugs in human skin. The resulting penetration has two possible implications for topical therapy:
- an increased therapeutic effect for any given concentration of an active constituent
- the attainment of a given therapeutic effect with a reduced concentration of the active ingredient.

Riassunto

Gli effetti esplicati dall'urea sono connessi alla sua penetrazione attraverso i differenti strati dell'epidermide e, quindi, direttamente dipendenti dal tipo di veicolo utilizzato. Per questi motivi sono state riscontrate differenze nella durata e nella intensità della capacità del prodotto di legare acqua in dipendenza del tipo di emulsione. Per incrementare l'idratazione cutanea e la capacità di legare acqua della cute affetta da patologie si sono dimostrate più efficaci concentrazioni di urea del 10% rispetto a concentrazioni del 2 o del 5%. Per uso cosmetico sono più adatte e sufficienti concentrazioni basse di urea.
L'urea può essere considerata una delle sostanze più attive nel promuovere la liberazione dei farmaci dai veicoli e, quindi, il loro assorbimento. Facilita, perciò, l'attività dei corticosteroidi, del ditranolo e di molti altri farmaci.
Queste sue caratteristiche ne consigliano l'uso terapeutico in due direzioni diverse:
-per incrementare l'effetto terapeutico di una data concentrazione di farmaci resi per questi motivi ugualmente attivi a concentrazioni più basse.

The use of urea in topical therapy and in cosmetics has undergone a revival in recent years (1, 3, 4, 11 and others).
Some reasons for this can be listed as follows:

1. By intensive basic research many properties of urea have been discovered and precisely defined. At the same time, the conditions for the therapeutic utilization of these properties e.g. problems of stabilization, have been delineated.

2. In topical therapy increasing use is made of pharmacokinetic information. The equal significance of the properties of the active substances and of the vehicle, the condition of the skin, and their mutual interactions, are not only recognized but also increasingly utilized a basic for overall therapeutic activity. Pharmaceutical formulations are selected and optimized in such a way that a desirable concentration/time profile is achieved for the substance in the appropriate skin layer.

3. The properties of urea itself make it ideal for external use, as it is a natural moisturizer and is well tolerated. As a physiological substance it is the end product of protein metabolism. In human skin its concentration is 1% and it is excreted in sweat in considerable quantities. After external or systemic administration it is not metabolized. No side effects, in particular non cases of sensitization or photosensitization, have so far been reported under therapeutic conditions.

Principles of the action of urea on skin

The penetration kinetics of urea, i.e. how much urea, in relation to exposure time, penetrates into individual skin layers after external application, are of decisive importance to the achievement of its effects. In relation to the vehicle, the penetration kinetics of urea show fundamental differences between w/o and o/w emulsions (7), and these yield different therapeutic effects.
Urea penetrates the horny layer of human skin more quickly from o/w emulsions than from w/o emulsions (Fig. 1). It should be noted that, at about 80%, the bulk of the urea which has penetrated is found in the upper horny layers.

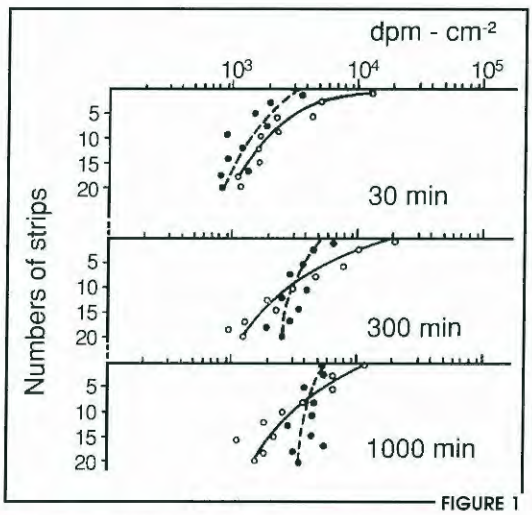

FIGURE 1

Distribution of urea in the horny layer of human skin after external application of 10% urea containing preparations.

•- - -• w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR)
o — o o/w-emulsion (Ungt. emulsificans aquosum, Pharmacopoea GDR)

The steep concentration gradient is largely maintained when o/w emulsious are used, even after as long as 1000 min.
In contrast, the penetration of urea from w/o emulsions is noticeably smaller after short exposure. The concentration gradient within the horny layer decreases so that after 1000 min approximately equal urea concentrations can be measured throughout the stratum corneum.
This results in different urea concentrations in the epidermis and dermis (Fig. 2), which are appreciably higher for w/o emulsions. Overall, however, the penetration of the lower epidermis and dermis are small in comparison with that of the horny layer, regardless of the emulsion used.

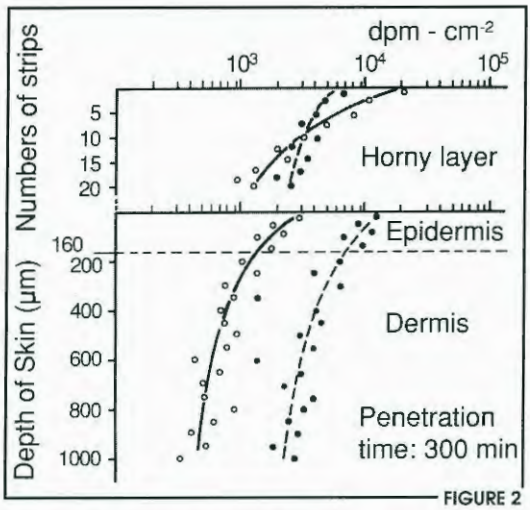

FIGURE 2

Distribution of urea in human skin after external application of 10% urea containing preparations.

•- - -• w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR)
o — o o/w-emulsion (Ungt. emulsificans aquosum, Pharmacopoea GDR)

These differences in the course of penetration and hence in the concentration/time profile of urea in the individual skin layer provide for different degrees of efficacy. Different emulsions can be used according to whether the urea is to act on the functional skin structure (e.g. hydration and water-binding capacity, keratolysis, inhibition of proliferation, alleviation of itching, etc.) or to aid penetration by other products.

What is the necessary concentration of urea in the vehicle?

From the findings so far discussed, it is clear that the decisive factor in therapeutic activity is not the concentration of urea in the applied vehicle but rather the quantity of urea which penetrates into the individual skin layers, i.e. the concentration/time profile achieved. It has be

Table I

CONCENTRATION OF UREA PENETRATING TO THE STRATUM CORNEUM (SC) OF HUMAN SKIN IN RELATION TO THE CONCENTRATION OF UREA IN THE VEHICLE (9)

Vehicle: W/O-emulsion (Ungt. Alcohol. Lanae aquosum AB-DDR)

Penetration Period (min)	Urea Concentration (%) applied	Urea concentration (mm) in the sc
30	2	29,9
	5	103,1
	10	212,6
300	2	48,3
	5	145,7
	10	449,9
1000	2	95,8
	5	231,6
	10	602,9

noted that, at around 80%, the bulk of the urea which penetrates is situated in the outer horny layers (Tab. 1). When vehicles containing 2% or 5% are used the urea concentration necessary for normal human stratum corneum cannot be reached. To increase the water-binding capacity in the horny layer of diseased skin products containing 10% of urea are more suitable from the therapeutic point of view (9). High urea concentrations (over 2-3%) are not, however suitable for cosmetic use without medical supervision.

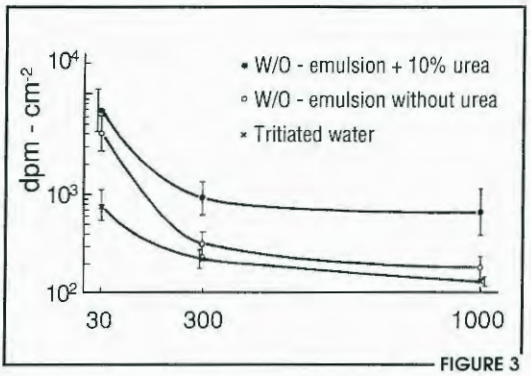

FIGURE 3

Influence of urea on the water-binding capacity of the human horny layer (10).
Vehicle: w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR) labeled with tritiated water.

Influence of the vehicle on the water-binding capacity due to urea.

Corresponding to the described differences in penetration, depending on the vehicle and the urea concentrations used, there are also variations in the effectiveness of the urea-containing basic skin products to increase the water-binding capacity of the stratum corneum (5, 6). When the urea is used in o/w emulsions or lotions, a high degree of hydration is quickly reached (immediate effect), but this fairly quickly declines (Fig. 3).
In contrast, with w/o emulsions there is a more market and longer-lasting increase in water-binding capacity.

Table II

WATER-BINDING CAPACITY OF HUMAN HORNY LAYER AFTER APPLICATION OF UREA CONTAINING PREPARATIONS (10).
Application: 10 mg of urea containing preparation labeled with 5 µCi tritiated water at 4 cm² skin surface.

preparation	urea concentration (%)	Horny layer dpm/cm2 after 30	300	1000 min
Basodexan (R) Ointment	10	5422 ± 521	2478 ± 205	902 ± 51
Basodexan (R) Cremé	10	8104 ± 514	1386 ± 169	472 ± 34
Basodexan (R) Soft	10	10606 ± 678	542 ± 98	185 ± 22
Carbamid-Cremé(R)	12	8666 ± 426	1214 ± 100	475 ± 28
Elacutan-F(R)	10	3968 ± 275	994 ± 63	678 ± 74
Elacutan-W(R)	10	7185 ± 376	426 ± 72	183 ± 19
Excipial(R)-U-Lotio	2	6804 ± 248	388 ± 26	126 ± 24
HTH(R)	10	12011 ± 528	568 ± 59	223 ± 63

If one examines these basic mechanism in relation to the various commercial urea-containing basic skin products, large differences are found in the action on the water-binding capacity of the stratum corneum (Tab. 2). These differences are evidently not primarily dependent on the urea concentration used but on the vehicle (10).

Influence of urea on the penetration of other products

Urea promotes the release of various drugs from their base, and in addition it is a very effective promoter of penetration of various active substances (1, 3, 4, 11). Essentially, the promotion of drug penetration by urea can be exploited in two ways (8):

1. to improve therapeutic efficacy at the same concentration of active substance and
2. to achieve the same therapeutic efficacy with a considerably lower concentration (Fig. 4).

The optimization of the therapeutic efficacy of other drugs by urea has been demonstrated above all with glucocorticoids (e.g. Hydrodexan (R), Hycozon (R), Alphaderm (R), etc.) and dithranol (e.g. Psoradexan (R)), with impressive evidence from numerous clinical studies.

With respect to hydrocortisone, it has been shown that when low concentrations of urea are used enhancement of penetration is barely apparent, whereas with a urea content of between 5% and 10% there is a particular increase (Fig. 5).

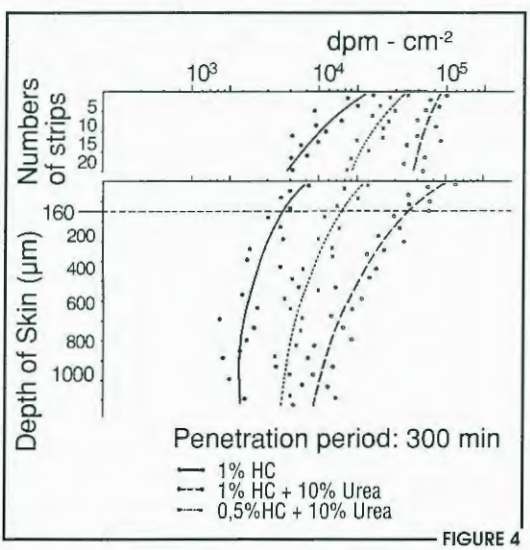

FIGURE 4

Distribution of hydrocortisone (HC) in human skin after external application (8).

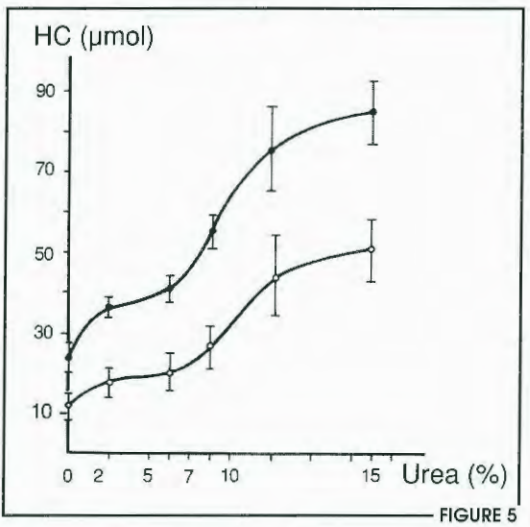

FIGURE 5

Dependence of hydrocortisone penetration into epidermis of human skin on urea concentration and used vehicle.
Penetration time: 300 min.
Hydrocortisone concentration: 1%
•- - -• w/o-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopoea GDR)
o o o/w-emulsion (Ungt. emulsificans aquosum, Pharmacopoeia GDR)

When the urea concentrations are raised further, no further decisive changes are detectable. In this connection o/w emulsions and w/o emulsions basically act in the same direction, but w/o emulsions have a considerably greater penetration-promoting effect.

On the basis of these data hydrocortisone, the determination of the penetration kinetics of the glucocorticoid and of the urea in each vehicle is indispensable for making use of the penetration-promoting action of urea in the development of

glucocorticoids for external use (8). The urea and glucocorticoid concentrations can then be optimized.

Less attention has so far been paid to the possibility of using the penetration-promoting action of urea to achieve a particular therapeutic efficacy with a considerably reduced quantity of glucorticoid. One reason is very probably the widely practised dilution of proprietary glucocorticoid formulations. In 1984 Müller (2) summarized the reasons for this procedure and its problems and risks in a very informative review. The example of hydrocortisone shows very clearly that after reduction to 0,5% the quantity which penetrates e.g. into the epidermis can be reduced by 75-80% (Tab. 3). In contrast, when various quantities of urea are added, a concentration-dependent promotion of penetration is detectable, so that the formulation becomes identical in efficacy with a 1% hydrocortisone product in which there is no urea.

Viewing this subject as a whole, we still know too little about the pharmacological properties of urea fot external use. Automatic procedures in the application of urea in external therapy and examination of the properties of urea in isolation therefore promise little success and should be avoided.

Table III

INFLUENCE OF UREA ON THE PENETRATION OF REDUCED HYDROCORTISONE CONCENTRATIONS INTO HUMAN SKIN (12).

Vehicle: W/O-emulsion (Ungt. Alcohol. Lanae aquosum, Pharmacopea GDR)
HC = hydrocortisone; U^+ = Urea.

Preparation	penetration time (min)	
	30	300
horny layer (mmol)		
1,0% HC	13,9	16,1
0,5% HC	2,9	3,9
0,5% HC + 5% U^+	8,5	10,0
O,5% HC + 10% U^+	12,5	13,8
0,5% HC + 15% U^+	12,8	14,0
epidermis (µmol)		
1,0% HC	12,8	23,2
0,5% HC	2,1	5,7
0,5%HC + 5% U^+	6,8	11,0
0,5% HC + 10% U^+	10,2	19,9
0,5% HC + 15% U^+	11,9	20,7

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