

A NEW TREATMENT OF ICHTHYOSIS AND OTHER HYPERKERATOTIC CONDITIONS

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The possibilities of treating ichthyosis and other hyperkeratotic states are today unsatisfactory. Little knowledge is available about the biochemical and physicochemical background of these conditions. The keratinized part of epidermis in ichthyosis is very dry and often thickened. Blank (1) pointed out the importance of the water content in the horny layer for the softness of the skin. The general opinion seems to be that watersoluble part of low molecular weight of the horny layer is the component responsible for keeping the water in the horny layer (1, 2, 5, 6). This function is quite different from the function of the so-called barrier zone (9, 10). In scaling dermatoses the state of aggregation of the epidermal keratin and lipids is different from that of the normal horny layer (7, 8). This may also be of importance for the water binding capacity of the horny layer or possibly secondary to it.

In cosmetic preparations hygroscopic substances like glycerol and sorbitol are often used. Such substances are however of very little use in the treatment of hyperkeratotic conditions. It seems to be necessary, when trying to get a hard and rough horny layer smooth and soft not only to increase the water content, but also to disperse the epidermal keratin. Softness and pliability of the horny layer must mean that there is a certain freedom of movement of the fibrous elements with respect to each other. To

achieve this an agent capable of dispersing epidermal keratin might be necessary. It is also possible that water binding groups or components may be exposed by a keratin dispersing agent.

From laboratory studies it is known that concentrated solutions of urea are very effective in dispersing epidermal keratin (4). Urea is furthermore not toxic or allergenic (3). A preliminary laboratory study concerning the effect of urea treatment on the water content of normal and pathological horny layer and a clinical study on the use of high concentrations of urea for the treatment of some dermatoses were performed. The results of these studies are reported in the present paper.

Material and Methods

For the investigation of the water binding capacity are used normal horny layer, psoriatic and ichthyotic scales. The normal horny layer was cut into pieces of about $0.5 \times 0.5 \times 3$ millimeters, and the scales were used as such. The specimens were immersed for twelve hours in distilled water, urea or glycerol solutions. Thereafter the specimens were blotted on filter paper and put in a glass chamber with specified relative humidity. The humidity was regulated by different saturated salt solutions in a large Petri dish in the glass chamber. The humidity was checked by a hair hygrome-

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ter. The values obtained with the different salt solutions were the following: potassium carbonate 58 percent, sodium nitrite 70 percent and sodium tartrate 85 percent. The specimens were removed from the chamber during a short time for weighing on a torsion balance. The water content of the specimens was estimated by weighing the specimens at a certain humidity and subtracting the weight of the specimen after drying for 24 hours in dry atmosphere. The water content was then calculated as percent of the dry weight. At a given humidity equilibrium was obtained after about twelve hours.

In the clinical experiment mainly outpatients were used. After a pilot experiment with a few patients, it was evident that a double blind study could not be carried out as the physician very easily could recognize the urea-treated side because of the softness of the skin on that side. The ichthyotic and psoriatic patients were treated with ten percent urea in either Tween 80 2.5 g, cetanolum 15 g, adeps lanae 15 g, methyl paraoxibenz. 0.2 g, aqua dest. ad 100 g or in Span 80 2.5 g, Tween 80 0.5 g, vaselinum album 47 g, aqua dest. ad 100 g. The patients with atopic eczema were treated with the same creams but with hydrocortison added in the amount of one percent. Generally the same creams without urea were used as controls. Four of the psoriatic patients used fluocinolon. acetone ointment¹ as control. Ten of the atopic patients used different commercially available hydrocortison ointments as controls. One side of the patient (left or right) was treated with the urea cream and the other side with the control cream or ointment. Nothing was said in advance to the patients about the expected effect of the urea cream. The time during which the treatment was followed varied between 5 days and 4 weeks.

Results

Laboratory Investigations

Normal horny layer from the foot sole starts taking up water at a relative humidity

(r.h.) of about 70 percent. At 85 percent relative humidity of about 11 percent of the dry weight had been taken up. In the samples used most of the water was taken up within five hours. The psoriatic and ichthyotic scales had not taken up any measurable amount of water at 85 percent r.h. If specimens of normal horny layer have been immersed for about 12 hours in a 35 percent solution (v/v %) of glycerin and dried, they took up 20 percent water at 85 percent r.h. Specimens immersed in 5 M urea and dried took up 34.2 percent water at 85 percent r.h. Psoriatic scales took up 22.8 percent water after glycerol treatment and 37.5 percent after treatment with urea under the same conditions. Ichthyotic scales treated with 5 M urea for about twelve hours took up 57.9 percent of water at 85 percent r.h.

To study the effect of combining urea and glycerol treatment one volume pure glycerol was added to two volumes of 5 M urea. After immersion of normal horny layer in this solution for about twelve hours and subsequent drying 26.0 percent of water was taken up at 85 percent r.h. Immersion of normal horny layer in 1 M solution of urea gave after drying an uptake of 14.3 percent of water at 85 percent r.h. The results of the laboratory investigation are summarized in *table 1*.

Clinical Investigation

The ichthyotic patients were selected so that both light and severe cases were included in the investigation. Two patients with ichthyosis laevis (a man aged 29 and a woman aged 38) had dry and rough skin mostly pronounced on the lower legs, hands and lower arms. The effect of urea cream on these patients was striking and after less than a weeks treatment the skin looked normal. The effect of the control cream without urea was not so good.

Two relatively severe cases of ichthyosis vulgaris (a boy aged 17 and one aged 20) were considerably improved by the urea cream but only slightly improved by the control cream. Two severe cases of ich-

¹ Synalar 0.025 %, ICI.

Table 1. Uptake of water at 85 % relative humidity (in percent of dry weight)

Treatment	Type of horny layer		
	Normal from foot sole	Psoriatic scale	Ichthyotic
1 M urea	14.3 %	—	—
5 M urea	34.2 %	37.5 %	57.9 %
35 % glycerol	20.0 %	22.8 %	—
glycerol+6 M urea	26.0 %	—	—
Dest. water	11.3 %	0 %	0 %

Table 2. Results of clinical trial. The figures indicate the number of patients

Diagnosis	Normal appearance of the skin	Soft skin with visible changes like erythema	Unchanged
Ichthyosis laevis	2	0	0
Ichthyosis vulgaris	0	2	0
Ichthyosis congenita	0	2	0
Ichthyosis linearis	1	0	0
Atopic eczema	4	8	0
Psoriasis	0	5	0

thyosis congenita (a man aged 69 and a woman aged 44) were greatly improved by the urea cream. The reptile like cornifications scaled off within a few days and the horny layer became smooth and soft. A pale erythema was seen after a weeks treatment. In these two cases the keratolytic effect of urea was convincingly demonstrated. The control side was practically unchanged. One six years old girl with ichthyosis linearis became practically free of symptoms after little more than a weeks treatment with the urea cream. The control cream had only a very slight effect. No adverse effects were noted among the ichthyotic patients treated with the urea cream. All patients in this group wanted to go on with the urea treatment and several of them expressed spontaneously that it was the best treatment they had had for their skin disease. In a few cases it turned out to be sufficient with treatment only after regular baths as seldom as once a week. Twelve patients (between 2 and 30 years of age) with atopic eczema were in-

cluded in the experiment. All the twelve patients became more soft and smooth in the skin on the urea treated side. Four of the twelve patients became clinically healed during a three weeks period of treatment while eight had slightly erythematous lesions left. In all cases a clinically better effect was obtained with urea cream containing hydrocortison than with the control hydrocortison cream or ointment. One patient had a burning or itching feeling for a short time after the application of the urea cream to freshly excoriated lesions. This is probably due to the fact that the water phase of the cream is hypertonic. All patients in this group wanted to continue with urea cream. The five psoriatic patients were chronic cases with large plaques. They had all tried different treatments (like fluocinolone acetonide ointment and dithranol paste) without effect. The urea cream gave a soft and pliable skin but the erythema was unchanged. No adverse effects were noticed. The clinical results are summarized in table 2.

Discussion

Urea was the first organic substance synthesized. It has been used in medical treatment in different ways. In dermatological preparations it has been used in low concentrations (3). Urea has some bacteriostatic activity. This is one of the reasons for its use in dermatology. One advantage of urea in dermatological preparations is that it is not allergenic. In laboratory work urea has been used as a dispersing agent for epidermal keratin (4). From laboratory work

it is also known that urea is very water soluble and can retain water at high relative humidities. When used in dermatological preparations it may be suspected that urea has both a water binding function and a keratolytic activity. The keratolytic activity is already known from *in vitro* experiments. In the present study it has been shown that urea treatment gives a high water binding capacity to the horny layer. The water binding capacity of the horny layer is considerably better when treated with urea than with glycerol only. It is notable that the addition of glycerol to a urea solution gives a lower water binding of the horny layer than if the urea solution alone is used for the treatment of the specimens. This phenomenon will be studied further and may indicate that the keratolytic effect of urea is more important than its hygroscopic properties. This is not contradicted by the fact that a low concentration of urea gives a very small increase in the water binding of the horny layer. It is of interest also to note that the water binding capacity of urea-treated psoriatic and ichthyotic scales is at least as good as in normal horny layer treated in the same way. The results of this preliminary laboratory study thus made it likely that high concentrations of urea might be of value in the treatment of dry and hyperkeratotic skin. Since ichthyotic patients have a dry and hyperkeratotic skin local treatment should therefore combine keratolytic and moisture retaining activity. The clinical experiments reported in the present paper show that the effect of urea cream on ichthyosis is very good. In the more severe cases the keratolytic activity was evident as well as the moisture-retaining activity, while in other cases the moisture retention in the horny layer was first observed. In atopic eczema and psoriasis the dominating effect of urea treatment is the softness of the skin. In the latter two dermatoses steroids have to be added to the cream in order to get good clinical results.

In general a high concentration of urea in a cream base seems to be preferable whenever a keratolytic agent is indicated. Besides being more effective than e.g. sali-

cyclic acid, urea does not have the disadvantages of being toxic or allergenic.

SUMMARY

The use of high concentrations (about 10 percent) of urea in creams is suggested for the therapy of ichthyosis and other hyperkeratotic conditions.

In a preliminary laboratory study it is shown, that such treatment increases considerably the uptake of water by the horny layer or by scales of ichthyotic and psoriatic patients from an atmosphere of 85 percent relative humidity.

Seven patients with ichthyosis of different severity were treated with urea cream. In the more severe cases a pronounced keratolytic effect was noticed. In all cases the skin became soft and pliable. Twelve cases with atopic eczema were treated with urea cream containing one percent hydrocortisone. All twelve patients became soft in the skin; the clinical result was better than using a one percent hydrocortisone ointment without urea. Five psoriatic patients with chronic therapy-resistant lesions were treated with a ten percent urea cream. All became soft and pliable in the skin, but the erythema was unaffected. A general impression was that urea is far more effective as a keratolytic agent than substances like salicylic acid. Urea also has the advantage of not being toxic or allergenic. The possible mechanism of the effect of urea on the horny layer is discussed.

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