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The Influence of Urea on the Penetration Kinetics of Topically Applied Corticosteroids

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The effect of urea on the penetration of hydrocortisone and triamcinolone acetonide into human skin from topically applied vehicles was studied. The resulting penetration promotion has two possible appications in topical therapy: (*a*) An increased therapeutic effect for a given concentration of the active constituent. (*b*) A given therapeutic effect could be obtained with a reduced concentration of the active ingredient. *Key words: Skin; Penetration; External therapy; Urea.* (Received June 10, 1983.)

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The success of any topical therapy depends upon obtaining an optimum concentration of the active therapeutic agents within the diseased dermal layer. The whole process is determined by the degree of *liberation* of those agents from the ointment and their *penetration* into the skin.

Thus it is essential in the preparation of ointments or creams that an appropriate concentration of the active agent is achieved and also that the galenic preparation is suited to the properties of that agent as well as to the dermatoses to be treated. However, many investigations have shown that a high percentage of topically applied agents do not penetrate into the skin, but may be removed from its surface even after some time (1, 2, 3); for hydrocortisone and triamcinolone acetonide this has been demonstrated to lie in the range 70–90% (4). The therapeutic effect of numerous topical preparations may be strikingly improved by the use of occlusion, which increases penetration of the active agents.

In the galenic formulation of topical preparations, little attention is paid to the fact that the horny layer's absorptive capacity for the agent may be considerably increased by influencing its structural-functional condition, and hence, by changing the penetration conditions the therapeutically effective concentration of the agent may be optimised.

The keratolytic and increased water-binding properties of urea make it a penetration promoter and able to change the functional structure of the horny layer (5). Therefore, we investigated the question of influencing the percutaneous penetration of various corticosteroids by adding urea to the topical vehicle.

MATERIALS AND METHODS

The investigations were performed on human skin taken from the inguinal region during lymphadenectomy procedures. Intra-operatively, the subcutis was removed, the skin cut into the unit areas required for the procedures and stored at −20°C for a short term period wrapped in aluminium foil. The methods described by Zesch & Schaefer (6) and Schaefer et al. (3) respectively, were employed.

Test substances

The following galenic preparations were tested:

1. 1% Hydrocortisone in w/o emulsion (Ungt. Alcohol. Lanae aquosum AB-GDR).

2. 1% Hydrocortisone plus 10% urea (Hydrodexan®).
3. 0.5% Hydrocortisone plus 10% urea (Hydrodexan® plus Basodexan® 1 : 1).
4. 0.1% Triamcinolone acetonide in w/o emulsion.
5. 0.1% Triamcinolone acetonide in w/o emulsion plus 10% urea adsorbed onto particles of polysaccharide (7).
6. 0.05% Triamcinolone acetonide in w/o emulsion plus 10% urea adsorbed onto particles of polysaccharide (7).

For radiolabelling these test preparations we used tritium labelled hydrocortisone and triamcinolone acetonide (1, 2, 6, 7-^{3}H) cortisol; specific activity 93 Ci/mmol ≙ 3.44 TBq/mmol; (1, 2, 4*n*-^{3}H) triamcinolone acetonide; specific activity 22 Ci/mmol ≙ 814 GBq; Radiochemical Centre, Amersham, with 25 μCi (=925 KBq) radioactive labelled substance being mixed into 50 mg of the corresponding ointment.

Exposition and penetration measurement

Details of the experimental procedure has been published elsewhere (8). About 16 mg of ^{3}H-labelled corticosteroid ointment were applied to the test area of 4 cm^2 skin by means of a spatula and distributed uniformly. The amount of steroid that had penetrated the skin was calculated as a percentage of the applied dose or in μg/cm^2 of the corresponding dermal layer according to our knowledge of the applied quantity of the substance, the specific activity, the area of stripped skin, the volume (area and thickness of the sections) of the histologic sections as well as the assignment to the various dermal layers.

RESULTS

The quantities of hydrocortisone determined in the corresponding dermal layer at different times from the various galenic formulations are summarised in Table I. For all ointments to be tested it can be concluded that the greater part of hydrocortisone is located in the horny layer irrespective of the penetration time.

The addition of 10% urea results in a considerable increase in the concentration of hydrocortisone within the horny layer, epidermis and dermis in the order of two to three-fold (see Table I). The increase seen after longer periods of penetration into the deeper layers of the dermis is due to a retention of the substrate as is frequently seen under these conditions in vitro (6).

The promotion of hydrocortisone penetration engendered by the addition of urea is especially obvious if a comparison is made between the results obtained with the 0.5% hydrocortisone plus 10% urea and the 1% hydrocortisone cream without urea (see Fig. 1). The steroid content obtained in both dermis and epidermis with the 0,5% hydrocortisone plus 10% urea cream is approximately 50% greater than that obtained with the 1% hydrocortisone cream without urea.

Similar changes were also demonstrated with triamcinolone acetonide (Table II). Here, too, the reservoir of the agent in the horny layer as well as the concentration within the epidermis and dermis after adding urea were considerably increased. Topical application of 0.05% triamcinolone acetonide plus 10% urea gave rise to similar concentrations as those achieved with creams containing twice the steroid content, but without urea.

DISCUSSION

The initial steps of any topical therapy are characterised (*a*) by the level of liberation of the drug from the ointment base concerned, and (*b*) by both the extent of penetration of the agent into the skin and its absorption into the different skin layers. From a pharmaceutical viewpoint, urea is of particular interest as it is known to considerably increase both the liberation of steroids from topical vehicles and by altering the functional structure of the skin to allow increased penetration of the steroid into the skin thereby enlarging the skin

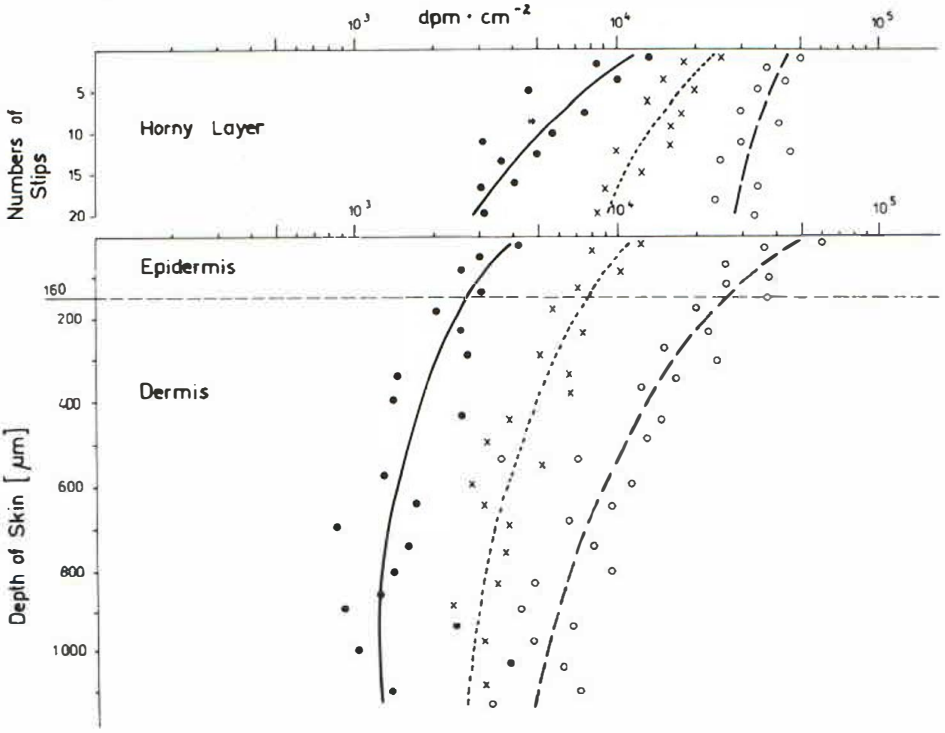

Fig. 1. Distribution of hydrocortisone in human skin after external application and penetration period of 300 min. ●—●, 1% hydrocortisone; ○–○, 1% hydrocortisone + 10% urea; × · · · ×, 0.5% hydrocortisone + 10% urea.

Table I. *Amount of hydrocortisone (in µg/cm² skin surface) in different skin layers after topical application*

HC = hydrocortisone; U^+ = urea

Skin layer	Penetration period (min)	1% HC	1% HC + 10% U^+	0.5% HC + 10% U^+
Horny layer	10	8.4	13.1	12.4
	30	10.9	18.5	14.3
	100	13.6	21.6	18.1
	300	11.7	24.1	17.3
	1 000	14.1	28.9	16.8
Epidermis	10	0.05	0.09	0.08
(<160 µm skin depth)	30	0.08	0.16	0.13
	100	0.12	0.25	0.19
	300	0.16	0.39	0.28
	1 000	0.15	0.41	0.26
Dermis	10	0.04	0.09	0.07
(>160 µm skin depth)	30	0.14	0.31	0.29
	100	0.20	0.52	0.34
	300	0.26	0.71	0.63
	1 000	0.24	0.71	0.54

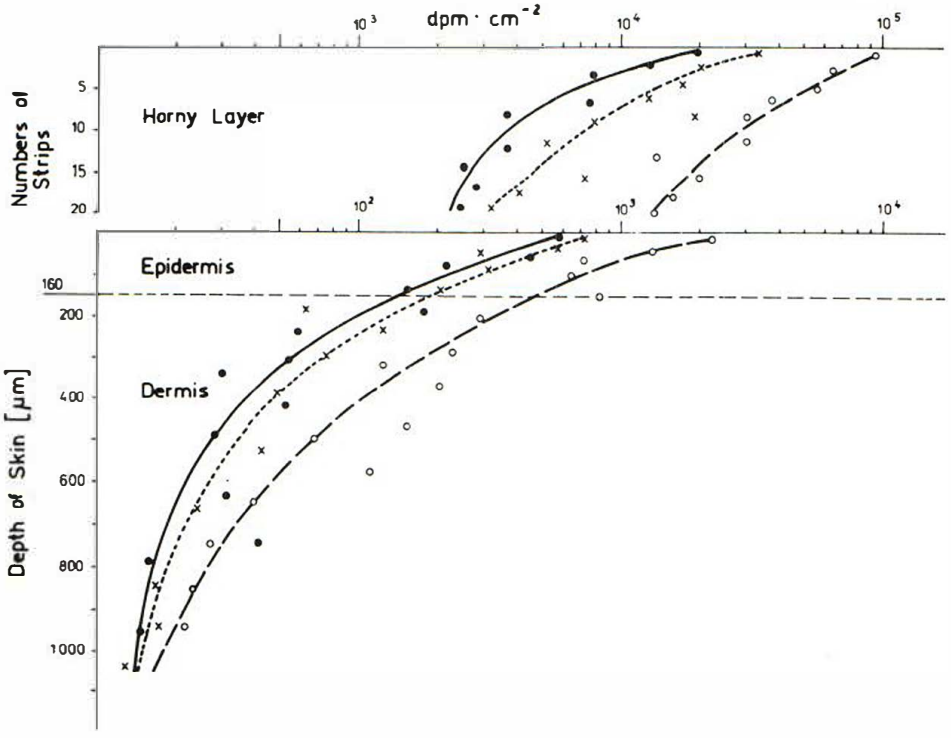

Fig. 2. Distribution of triamcinolone acetonide in human skin after external application and a penetration period of 300 min. ●—●, 0.1% triamcinolone acetonide; ○--○, 0.1% triamcinolone acetonide + 10% urea; × · · · ×, 0.05% triamcinolone acetonide + 10% urea.

Table II. *Amount of triamcinolone acetonide (in µg/cm² skin surface) in different skin layers after topical application*

TA = triamcinolone acetonide; U^+ = urea

Skin layer	Penetration period (min)	0.1% TA	0.1% TA + 10% U^+	0.05% TA + 10% U^+
Horny layer	10	0.42	1.31	0.66
	30	1.23	2.66	1.47
	100	1.35	2.79	1.61
	300	1.60	2.81	1.62
	1 000	1.58	2.69	1.64
Epidermis (<160 µm skin depth)	10	0.14	0.19	0.16
	30	0.26	0.39	0.28
	100	0.31	0.53	0.33
	300	0.34	0.61	0.38
	1 000	0.38	0.59	0.23
Dermis (>160 µm skin depth)	10	0.08	0.15	0.10
	30	0.12	0.31	0.14
	100	0.20	0.33	0.16
	300	0.19	0.36	0.09
	1 000	0.26	0.30	0.12

reservoir for that steroid (9, 10). Thus, urea is one of the most effective penetration promoters (7).

The mechanism of this penetration promotion by urea can be attributed to the interaction of several factors. Corticosteroid solubility is increased by urea (7). Other workers have shown that penetration rate and clinical effectiveness are dependent upon the vehicle used and the steroids solubility in it (11, 12). Different effective concentrations in the vehicle, however, do not lead to remarkable changes in the penetration rate (13). Increases in the steroid concentration in the vehicle up to 1% result in proportional increases in steroid content in the skin; doubling the concentration of hydrocortisone above 1% leads to an increase of the effective amount within the tissue of only about 40–50% (13).

The penetration promotion of corticosteroids by means of urea can be utilised in topical therapy from two different points of view:

1. By adding urea to appropriate ointments of corticosteroids an improved therapeutic effect may be achieved by increased penetration into the skin with the same effective concentration. This principle has been already applied to various preparations of hydrocortisone and successfully used in several studies because of its clinical effectiveness (2, 11, 14, 15). Experimental proof whether changes in the effective penetration of halogenated corticosteroids other than triamcinolone acetonide is lacking (Table II, Fig. 2); these changes for triamcinolone acetonide result in an increased therapeutically effective drug concentration within the living layers of the skin. This is likely since even with triamcinolone acetonide about 70–90% of the applied dose remains on the surface of the skin and a normal horny layer can only store up to 30% of the steroid (4). Both facts can be influenced by the effect of urea.

2. To reach the same therapeutic efficacy much smaller drug amounts may be applied and accordingly increased drug concentrations in the dermal layers can be obtained by penetration promotion with urea. Consequently, when using a 0.05% triamcinolone acetonide preparation with the addition of urea, nearly the same concentrations may be achieved in the various dermal layers as with double the amount of corticosteroid without the addition of urea (Table II). We were able to demonstrate similar results using dithranol (data not yet published). A reduction of side-effects with corticosteroids cannot be expected, however, if such a reduction was obtained with dithranol it would be important clinically.

When comparing the drug concentration from a 1% ointment of hydrocortisone measured within the epidermis with that of a 0.5–1% ointment of hydrocortisone with the addition of urea (Table I) it becomes obvious that the concentration of the agent is increased by about 70% and 120% respectively. According to Krantz et al. (13), a doubling of the concentration of hydrocortisone—even with addition of urea of less than 1%—just as with higher amounts of the agent—will lead to a non-linear increase of drug concentration within the tissue. It remains to be seen to what extent the favourable therapeutic results with 1% ointments of hydrocortisone/urea may also be achieved with lower concentration of hydrocortisone. From these points of view initial experiences with hydrocortisone, triamcinolone acetonide and dithranol seem to indicate further possibilities for the application of urea in topical therapy.

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