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# An Experimental Study of Irritant Effects of Urea in Different Vehicles

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**The properties of urea as an irritant were investigated. Seventeen healthy volunteers were patch tested with 20% urea using petrolatum and water, respectively, as vehicles. Irritant effects of urea were assessed by clinical evaluation of patch test reactions as well as by various non-invasive methods. The inflammatory response was quantified by laser Doppler flowmetry measuring the superficial blood flow, and by ultrasound A-scan reflecting the edema formation. Impairment of the barrier function was indicated by measurement of transepidermal water loss (TEWL). It is concluded that 20% urea in petrolatum applied under occlusion for 24 h elicits significant inflammation (i.e. increase in blood flow and skin thickness) and causes impairment of the skin barrier (i.e. increased TEWL). The irritant impact of urea on the skin depends upon the vehicle used, the irritant effect being intensified when urea is dispensed in petrolatum compared with water.**

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Urea is widely used in dermatological products by virtue of its moisturizing, keratolytic, desquamating, anti-pruritic and antimicrobial characteristics (1,2). Due to its low molecular weight, urea has a strong osmotic effect and increases the water binding capacity of the skin. Since a well hydrated stratum corneum appears to improve the barrier function of the skin (3,4), it is of great importance. The effect of urea on the barrier function of the skin has however been debated, and some authors have found that urea impairs the water barrier function of stratum corneum (3,5). The potentiality of urea as a primary irritant has also been considered. In 1943, Rattner (6) patch tested 500 individuals with 3% urea and found no positive reactions. Cramers & Thormann (7) patch tested 79 individuals with Calmuril cream (10% urea and 5% lactic acid in a water base), and found 7 positive reactions; another 5 subjects had erythematosus reactions.

To further elucidate the properties of urea as an irritant on human skin the present study was undertaken. To elicit an irritant response, urea was applied to the skin under occlusion using a patch test system. Since the efficacy might to some extent depend upon the base used (8,9), both petrolatum and water were used as vehicles. The effect of urea on the skin was assessed by clinical evaluation and by various noninvasive, bioengineering methods reflecting both the inflammatory response (blood flow and oedema), and the barrier function of the skin.

## MATERIAL AND METHODS

Seventeen healthy volunteers participated in the study: 13 males and 4 females, median age 28 years (range 22–46). Informed consent was obtained from all volunteers, and the study was approved by the local medical ethics committee.

The flexor side of the upper arm was chosen as test region and closed patch tests were applied using large Finn chambers (diameter 12 mm, Epitest$^R$, Helsinki, Finland) on Scanpore$^R$ tape. The placement of the chambers was randomized and "blinded" to the examiner. Urea 20% in water and 20% in petrolatum were used as test substances. Identical quantities of urea were used in both vehicles. Test chambers with water and petrolatum served as controls. Test chambers were removed after 24 h. Patch test sites were evaluated prior to patch testing (pre-values) and after 24 h (60 minutes after removal of chambers) and 48 h.

Visual scoring was performed according to the following scale: 0, no reaction; ½, scaling or very week erythema; 1, weak erythema, possible slight infiltration; 2, marked erythema, infiltration, possibly vesicles and crusting; 3, pronounced erythema, infiltration, possibly vesicles, bullae, pustules and/or pronounced crusting.

A laser Doppler flowmeter (Periflux Pf$^R$) was used to quantify the cutaneous blood flow (10). The light from the laser is led by an optical fibre to the skin surface. The Doppler-shifted light is back-scattered from moving blood cells, while unshifted laser light is back-scattered from stationary tissues. The instrument was adjusted to a bandwidth of 12 kHz and a gain of 10. The output signal was expressed in relative and dimensionless blood flow values (a.u.). The laser Doppler probe was held gently against the skin to avoid vascular compression, and readings were made as average values after stabilizing the level.

Skin thickness was measured with a 20 MHz A-mode pulsed ultrasound scanner (Dermascan A$^R$, Cortex Technology, Hadsund, Denmark) (11). By measuring the distance between the acoustic echoes from stratum corneum and those from the dermis/subcutis interface, respectively, the thickness of epidermis and dermis together could be determined. Values were expressed in mm. To calculate skin thickness, an acoustic velocity of 1580 m/sec was used.

Transepidermal water loss (TEWL) was measured with an evaporimeter (Servo Med$^R$ EP1) (12). The probe incorporates an open chamber 12 mm in diameter, and is equipped with hygrosensors for determination of temperature and relative humidity. TEWL is calculated automatically and expressed in g/m$^2$h. During all the measurements, the probe was hand-held, using an insulating glove, thus avoiding heating of the probe. Mean values were read during the period 30–45 sec after application of the probe onto the skin. A protection cover (no. 2107, supplied with the Evaporimeter) was used.

All visual scores and instrumental recordings were performed by one and the same investigator. Each measurement was expressed as the median value of three recordings. Measurements were performed with the arm held on a level with the heart. The subjects rested for approximately 20 min before measuring commenced. The study was carried out in May and September 1988, the temperature in the laboratory was kept in the range 19–21°C. An attempt was made to avoid air convection or any disturbances in the laboratory.

### *Statistics*

Wilcoxon's test was used for comparing median values of responses. The chosen level of significance was $p<0.05$.

## RESULTS

The results of the clinical evaluation of the patch test reactions are given in Table 1. A visible reaction occurred significantly more often to urea/petrolatum patches than to urea/water patches ($p<0.001$)

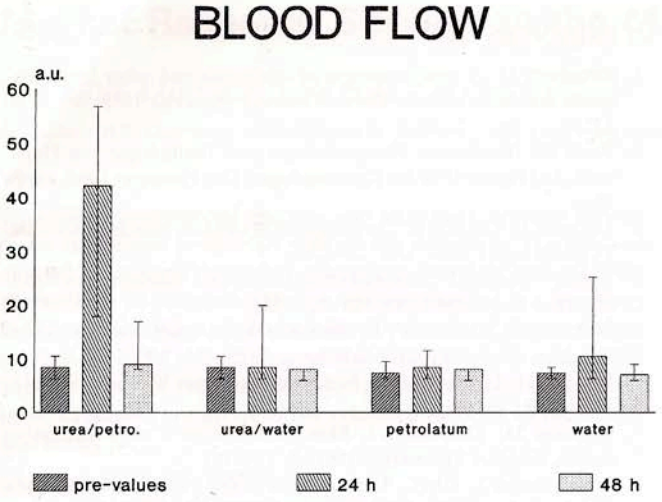


*Fig 1.* Superficial blood flow as measured by laser Doppler flowmetry for urea/petrolatum patches, urea/water patches, petrolatum patches, and water patches, respectively. Median values and 25/75 percentiles of pre-values, 24 h and 48 h measurements are given in arbitrary units (a.u.).

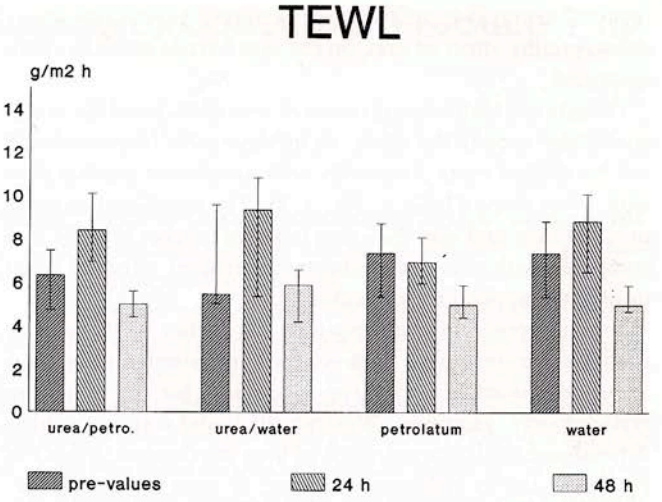


*Fig 3.* Transepidermal water loss (TEWL) as measured by evaporimetry for urea/petrolatum patches, urea/water patches, petrolatum patches, and water patches, respectively. Median values and 25/75 percentiles of pre-values, 24 h and 48 h measurements are given in $g/m^2$ h.

*Parameters of inflammation*

A significant increase in cutaneous blood flow was found in patches with urea/petrolatum after 24 h, both as compared with pre-values, and vis-à-vis the petrolatum control ($p<0.01$), (Fig.1). Blood flow was normalized after 48 h. No increase in blood flow was observed when using urea/water patches, whereas a significant increase in blood flow was evident in water patches after 24 h as compared with pre-values ($p<0.05$).

Cutaneous edema was found after urea/petrolatum patches after 24 h, skin thickness differing significantly from the pre-value and the petrolatum control value ($p<0.01$), (Fig.2). A significant increase in skin thickness after 24 h was also found for urea/water patches vis-à-vis the pre-value ($p<0.01$), but not as compared with the water control value ($p>0.05$). A significant increase in skin thickness was found in water patches after 24 h, as compared with pre-values ($p<0.05$).

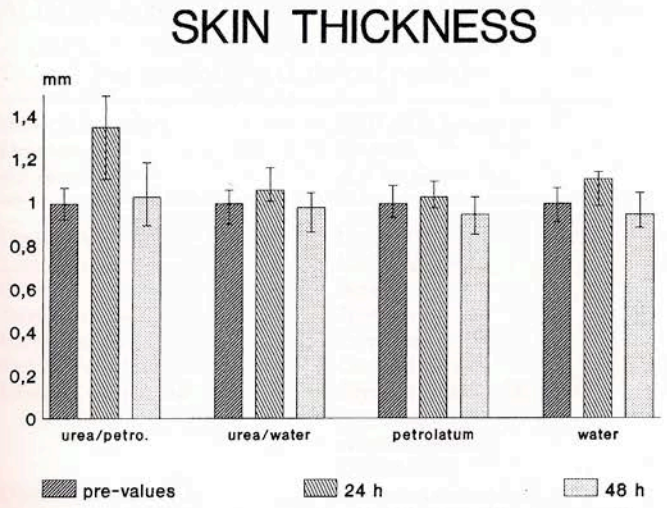


*Fig. 2.* Skin thickness as measured by 20 MHz A-mode ultrasound for urea/petrolatum patches, urea/water patches, petrolatum patches, and water patches, respectively. Median values and 25/75 percentiles of pre-values, 24 h and 48 h measurements are given in mm.

*Barrier function*

A significant increase in transepidermal water loss was found in patch test areas with urea in petrolatum after 24 h, as compared with pre-value ($p<0.05$) and petrolatum control ($p<0.01$), (Fig.3). TEWL values were normalized after 48 h. No significant increase in TEWL value was found for urea/water as compared with pre-value and water control.

## DISCUSSION

From the present study it can be concluded that 1) 20% urea in petrolatum applied under occlusion for 24 h causes significant inflammation (i.e. an increase in blood flow and skin thickness) and also influences the skin barrier (i.e. increase in TEWL); 2) these changes are transient and normal values are restored within 24 h; 3) the irritant impact of urea on the skin depends upon the vehicle used, the irritant effect being more intense when urea is dispensed in petrolatum than in water.

The impairment of the skin barrier function, caused by urea, paralleled the inflammatory response. Normal values were

Table 1. *Clinical evaluation of patch test reactions.*

| Scoring | Urea/pet. | Urea/wat. | pet. | wat. |
|---|---|---|---|---|
| 0 | 5 | 13 | 16 | 13 |
| ½ | 2 | 1 | 1 | 2 |
| 1 | 8 | 3 | 0 | 2 |
| 2 | 2 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 |

Total number of patch test reactions scored as 0, ½, 1, 2, 3 for urea/petrolatum patches, urea/water patches, petrolatum patches and water patches, respectively.

restored within 24 h, and in the present investigation no severe disintegrating effect of urea on the skin barrier could be demonstrated.

Despite the high concentration of urea (20%) and the occlusive design used in the study, an inflammatory response could not be elicited more frequently with urea/water patches than with water alone (Table 1, Fig. 1, 2). The significant increase in blood flow and skin thickness in water patches after 24 h as compared with prevalues indicates an irritant effect of water itself when applied under occlusion.

The difference in skin response in relation to the vehicle used is surprising, since both vehicles are assumed to be therapeutically inactive and serve as carriers for the active ingredient only. However, Wohlrab (9) found a strong vehicle dependence for the penetration of urea into human skin: O/W emulsions led to high concentrations of urea in stratum corneum and a low concentration in epidermis/dermis, compared to W/O emulsions which produced relatively higher concentrations of urea in epidermis/dermis. This observation that W/O emulsions more easily penetrate into the dermis than O/W emulsions, might explain the difference in inflammatory response between urea/petrolatum and urea/water patches. For clinical use where the irritant effect is undesirable, urea in aqueous emulsions are therefore preferable.

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