Urocanic acid in photodermatology
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One of the suggested mediators of ultraviolet-induced immunosuppression is cis-urocanic acid (cis-UCA), that is formed in the epidermis by photoisomerization of trans-urocanic acid (trans-UCA) [1]. In animal models cis-UCA has shown immunosuppressive effects, including the suppression of both sensitization and elicitation of contact allergy. Since cis-UCA is a low molecular weight compound (enabling it to penetrate into the skin) it might be an interesting topical agent for therapeutic use in a variety of dermatoses where immunosuppression is needed. With great interest we read the contribution of van Strien & Korstanje [2] who demonstrated a suppressive effect of topical UCA in treatment of allergic contact dermatitis in human volunteers.

Coincidently, we completed a preliminary study with comparable experiments, using an extended protocol developed earlier for use in the study of possible efficacy of topical cyclosporin in atopic eczema and allergic contact dermatitis [3]. In brief, patients known to be sensitized to nickel, perubalsam,
quinoline-mix or fragrances were patch tested with the respective compounds according to a modified ICDRG protocol. We studied the possible efficacy of cis-UCA in suppressing the contact allergic response, using trans-UCA and vehicle as a controls. Patch test sites were pretreated for 48 hours with cis- or trans-UCA (1% and 0.01% w/v) in 1% carbomer gel (vehicle), prior to the application of allergen, which was present for 72 hours under occlusion without the simultaneous application of a UCA-isomer.

Our results indicated that neither isomers had any effect in preventing elicitation in 4 individuals sensitized for fragrance mix, perubalsum and quinoline mix. In contrast to the findings of van Strien and Korstanje, we found that only in one out of 7 nickel sensitized individuals, did pretreatment with cis-UCA moderately suppressed the severity of dermatitis. In three out of 7 individuals both cis- and trans-UCA showed moderate suppression of elicitation as compared with control patches treated with vehicle alone. In the three remaining individuals no suppression was found with either UCA-isomers. Since the suppressive potential of trans-UCA did not substantially differ from cis-UCA in this respect, the immunosuppressive capacity ascribed to cis-UCA is not very plausible. Unfortunately, van Strien and Korstanje [2] did not include trans-UCA as an important control, making it difficult to interpret their results properly. We suggest that both UCA-isomers might have functioned as a chelating agent for nickel under these conditions. Chelation may prevent the availability of free nickel ions to initiate allergen formation with epidermal macromolecules. To that end, we investigated whether the lack of suppressive ability was caused by inefficient penetration of cis-UCA, although it was topically applied in excess. We determined the epidermal concentrations cis- and trans-UCA before and after a load of 48 h under occlusion of 1% cis- and trans-UCA in carbomer gel. Using a filter sampling method and HPLC-analysis [1], basic epidermal tissue levels of cis- and trans-UCA were found to be increased (about 8 times) under these conditions, indicating that an effective penetration of UCA-isomers in the epidermis of our volunteers had occurred.

To load the epidermis with increased amounts of UCA isomer requires a certain period of time to elapse. We can assume that the application of UCA isomers immediately before the application of the allergen may have the consequence that the migrating allergen is not surrounded by excess cis- or trans-UCA in the epidermis. In contrast, in our protocol UCA isomers are present in excess at the time of elicitation and this might favor the study of the possible suppressive effects of cis-UCA, and eventually, trans-UCA as well.
We conclude that cis-UCA, and also trans-UCA, could suppress some, but not all of the elicitation of nickel contact allergic reactions by chelation of nickel ions. Neither cis-, nor trans-UCA were effective in suppressing elicitation responses to other contact allergens. In this respect, neither isomer forms interesting compounds for further development as therapeutic agent in immune-mediated dermatoses.

References


Our results indicated that neither isomers had any effect in preventing contact allergic reactions to Nickel. In fact, we found that only in one out of 10 nickel sensitized individuals did pretreatment with a 5% UCA successfully prevent a reaction to Nickel. This suggests that the suppressive potential of trans-UCA did not substantially differ from any UCA in this respect, the immunosuppressive capacity ascribed to cis-UCA is not very plausible. Unfortunately, van Slooten and Konings [1] did not include trans-UCA as an important control, making it difficult to interpret their results properly. We suggest that both UCA isomers might have functioned as a chelating agent for nickel under these conditions. Chelation may prevent the availability of free nickel ions to initiate allergen formation with epidermal macromolecules. To that end, we investigated whether the lack of suppressive ability was caused by an efficient penetration of the UCA, although it was topically applied in excess.

We determined the epidermal concentrations cis- and trans-UCA before and after application under occlusion of 1% UCA and trans-UCA in cas-
ter plus gel using a thin sampling method and HPLC analysis [1]. Basic epidermal tissue levels of cis and trans UCA were found to be increased after 6 times under these conditions, indicating that an effective penetration of the isomers in the epidermis of our volunteers had occurred.

To load the epidermis with increased amounts of UCA isomers requires a certain period of time to elapse. We can assume that the application of UCA isomers simultaneously before the application of the allergen may have the consequence that the irritating allergen is not surrounded by excess cis- or trans-UCA in the epidermis. In contrast, in our protocol UCA isomers were present already at the time of elicitation and this might favor the onset of the possible suppressive effect of cis-UCA, and eventually, trans-UCA.