

Variation in response of human skin to irritant challenge

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A major obstacle to the establishment of a protocol for in vivo irritant skin testing in humans is the apparent variability of responses between individuals. This study of the threshold response of normal human skin to a standard irritant (sodium lauryl sulfate 0.3–10%), in a group of 22 subjects, revealed a marked interindividual variation in their threshold reaction. The results demonstrate that this phenomenon does exist and that it will have to be allowed for in future human irritant test systems or assays.

Key words: irritant contact dermatitis; sodium lauryl sulfate; human in vivo testing; patch test; interindividual variation; Draize rabbit skin irritation test. © Munksgaard, 1996.

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The standard and legally accepted method for detecting the hazard potential for skin irritancy of new and existing chemical substances and preparations is the modified Draize test (1). This assesses the degree of erythema and oedema (at 1, 2 and 3 days) at intact sites on the shaved backs of albino rabbits, following semi-occluded application of the undiluted test substances for 4 h. Various modifications of this test have been introduced and other animal assays have been proposed. However, the trend is away from the use of animal models and, indeed, the relevance of animal assays to the human skin irritancy potential of a substance has been questioned (2–4).

Therefore, predictive irritant assays are now being investigated (4–6). It is recognized that several variables have to be taken into account, such as the vehicle used in testing, the duration and number of applications, the type of occlusion, the site used, etc., but thought also has to be given to the possibility of intrinsic variation in response to irritants within the normal human population.

This study was designed as a preliminary evaluation of naturally occurring interindividual variation in the threshold response of human skin to occluded application of a standard irritant, sodium lauryl sulfate.

Materials and Methods

22 volunteers (8 females, age range 25–75 years) of skin type I–III were tested. 10 had no skin disorder and 12 were being assessed for dermatitis other than atopic, limited to the face or hands. Subjects with a history of atopy were excluded. No topical treatments were being applied to the test site. Occluded patches of sodium lauryl sulfate (SLS 99%) (BDH, Poole, UK), at dilutions in distilled deionized water of 0.3%, 1%, 3% and 10%, were applied in volumes of 0.2 ml in plastic-backed 25-mm Hill Top chambers to the upper outer arm for 4 h and then removed. The sites were examined at 1, 2 and 4 days, the reactions graded 0 (absent), + (mild), ++ (moderate) and +++ (marked) each for erythema, oedema and surface damage (scaling/erosion), and a total overall score derived. Sites were examined by 4 clinicians, agreement being sought when possible by reactions being read by more than 1 observer.

Results

19 of the 22 subjects produced a positive response at some concentration, whilst 3 were negative to all concentrations. Of the 19 positive reactors, the

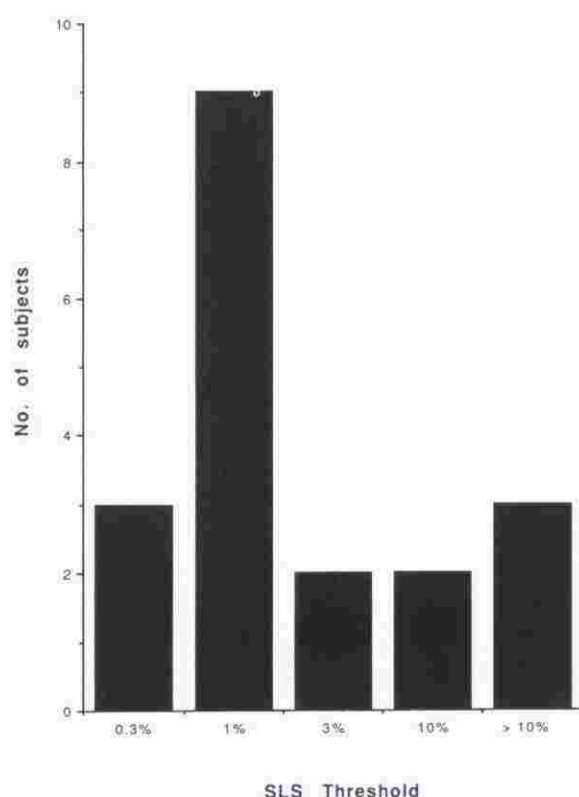


Fig. 1. Threshold of SLS in non-atopic subjects (n=19)

threshold response occurred at 10% in 2 subjects, 3% in 5, 1% in 9 and 0.3% in 3 (Fig. 1). The reaction to the 10% SLS patch test was mild (+) in 12 subjects, moderate (++) in 5 and strong (+++) in 2. These latter 2 and 1 moderate reactors all had an irritant reactions to 0.3% SLS, as well as to higher concentrations.

In positive reactions, maximal erythema occurred at 1–2 days, maximal oedema at 2 days and maximal surface damage at 2–4 days. 2 responders had a stronger reaction at the 3% patch test site than at the 10% test site. There was no difference in the threshold reaction or in the number of mild reactors between those with normal skin and those with a pre-existing skin disorder.

Discussion

A prototype human assay for the identification and classification of skin irritancy potential has already been described by Basketter et al. (4). Limited study of this approach, utilizing phased increases in the duration of occluded application of 20% sodium lauryl sulfate (SLS), suggested variation in the threshold time at which irritation observed. Ultimately, 13 of the 24 subjects demonstrated an irritant reaction at 1, 2 or 3 days to 20% SLS applied for periods of up to 4 h. This protocol

was designed to provide a positive control against which a test substance could be compared. As such, to correlate with previous animal studies, a visual scoring method was used.

The study described here demonstrated that significant variability in the threshold irritant response to standard concentrations of a known irritant, SLS, occurs in the general population. 12 of the 19 positive reactors had a threshold concentration for a reaction of 1% or less, and this high reaction rate may be related to the use of occluded patch tests. The range of reactions to SLS 0.3–10% seems to fall into an approximation of a normal distribution pattern, with 3 subjects each producing either no reaction to any concentration of SLS or an irritant reaction to 0.3% SLS. This population variation will need to be addressed in the development of an acceptable standardized human patch test protocol for ascertaining the irritation potential of a substance. Several systems, designed to overcome these limitations, are currently being assessed (5).

In the development of a human test for irritants that could replace the Draize test, it is important to devise a system that corresponds to traditional animal testing; therefore, we have used a 4-h exposure test under occlusion. As animal irritancy screening tests have been performed visually, this method of reading tests has been retained. The predictive tests of repeated irritancy (7) or of measuring by TEWL (7) have not been used, as both would be too far removed from animal tests, and the relevance of increased TEWL in the absence of visual erythema is not established. The upper arm has been used as a convenient site for irritancy testing; the same site should be used, as there can be interindividual variation between different sites in their threshold tolerance of irritants (8).

The marked variability found in this study is consistent with previous studies. Willis et al. (9), for example, found that 8/25 (31%) of subjects responded to 1% benzalkonium chloride applied for 2 days, and that 2 of these were exceptionally severe. Sex (10), age and skin type/colour (11) may also be important factors, and these factors are currently being analysed in a larger study.

The factors governing individual responses to irritants are poorly characterized, but it is likely that barrier function, which is mainly related to epidermal lipid composition, and one's genetically determined potential for epidermal cytokine release, both play an important rôle in an individual's susceptibility and response. Variability in penetration of SLS through the skin has already been demonstrated (12). The use of pure-bred laboratory animals in current test systems ensures a uniformity of response that cannot be expected in human sub-

jects. This necessitates the use of a suitable positive control in any human protocol intended as a replacement for the Draize rabbit skin irritation test.

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