

Facial variations in sensory responses

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Subjective effects such as stinging, itching and burning commonly occur in the absence of any visible irritation and give rise to discomfort, which may be enough to deter an individual from using even the most effective of skin care products. The purpose of this study was to evaluate the sensitivity of different anatomical regions of the face to determine which region displayed the most intense stinging response to the application of lactic acid. The effect of occlusion on the level of response was also investigated. 45 volunteers were treated with 10% lactic acid on the nasolabial fold, forehead, chin and cheek, occluded and unoccluded for 8 min. Sensory reactions were recorded at 2.5, 5 and 8 min. The response levels on the occluded sites were always significantly lower than on the unoccluded sites, despite the dose per unit area being comparable. Females showed a trend towards being more sensitive to the subjective effects elicited by lactic acid than males, but these results were not conclusive. Interestingly, there was not a complete correlation between individuals who reacted on the nasolabial fold and the other sites, particularly the forehead. A positive stinging response on the nasolabial fold may not necessarily predict subjective responses to a product when used on other areas of the face.

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The visual and physical effects of contact dermatitis can be debilitating and are acknowledged as such. Nevertheless, subjective (sensory) effects such as stinging, itching and burning, which commonly occur in the absence of any visible irritation, also give rise to discomfort and may be enough to deter an individual from using even the most effective of skin care products. This could be of particular concern where the products form a key element of an occupational skin care programme. There are various well-established methods for investigating skin irritation, e.g. conventional patch tests and exaggerated-use tests, the human 4-hr patch test and the cumulative irritation assay (1–4). In contrast, methods for most other types of skin reactions, including urticaria, burning, itching and stinging, are much less well established, although as indicated they are also of importance.

In practice, only the sting test developed by Frosch and Kligman (5) has gained any widespread use in the identification of products with a potential to elicit sensory responses. This assay has been investigated in some detail and has undergone a certain amount of modification over the years (6, 7). However, the sting test does not actually provide a surrogate for a wider range of sensory

effects, nor does it provide a general indicator of 'sensitivity' or of 'sensitive skin' (8–10). Indeed, the correlation between stinging in the nasolabial fold with that on other skin sites has been studied only to a limited extent. Stinging has been identified as a predominantly facial phenomenon (5, 8), and differences in the sensitivity of various regions on the face have been demonstrated (5–7). Some suggest the nasolabial fold to be the most sensitive area (5), whilst others propose the malar eminence (6), while the chin and forehead are suggested to be less sensitive and the upper lip has also been employed (7). In the present study, the sensitivities of different facial anatomical regions were compared, and the effect of occlusion on the level of responses was investigated. The primary purpose was to identify the effect of these variables on the sensitivity of the sting test, with a view to optimizing our standard test procedure, so enhancing its utility, sensitivity and predictivity.

Materials and Methods

Study population

45 healthy Caucasian adults, 17 males and 28 females, aged 18–57 years (mean age: 36 years)

were enrolled in the study after providing written informed consent. The panellists were asked to determine their skin type with respect to sun sensitivity as follows: type 1, always burns, never tans; type 2, usually burns, sometimes tans; type 3, sometimes burns, usually tans and type 4, never burns, always tans. The volunteers were recruited from Unilever staff at the laboratory site. Prior to the start of the study, the panellists were advised on the definition of several different sensory effects to aid distinction between the different sensations. Itching was described as the desire to scratch, burning was described as the painful sensation that follows a thermal burn and stinging was equated to the sensation that occurs when alcohol is applied to a cut or abrasion. These descriptions were made available to panellists at each application time. The test method was approved by the local ethical review committee prior to the start of testing.

Materials

10% a.i. (w/v) lactic acid was prepared in ultrapure water from an 85% racemic D-L syrup obtained from Sigma Chemical (Poole, Dorset, UK).

Open application of 10% lactic acid

10% lactic acid was rubbed briskly over 1 nasolabial fold of each panellist, ultrapure water being rubbed over the contralateral nasolabial fold. The panellists were asked to complete a questionnaire during treatment at 0, 2.5, 5 and 8 min detailing the type and intensity of any sensory effects experienced utilizing a 4-point scale (none = 0, slight = 1, moderate = 2 and severe = 3). The chin, forehead and malar eminence were also tested in this manner on separate occasions, an area approximately the diameter of the Hilltop chamber (HillTop Companies, Cincinnati, OH, USA) was treated.

Occluded application of 10% lactic acid

50 µl of 10% lactic acid was applied to the chin, forehead and malar eminence (cheekbone area) via a 25 mm Hilltop chamber (HillTop Companies), which was held in place by 2 short pieces of Scanpor® tape (Norgesplaster A/S, Vennesla, Norway). The panellists were asked to complete a questionnaire during treatment at 0, 2.5, 5 and 8 min, detailing the type and intensity of any sensory effects experienced utilizing a 4-point scale (none = 0, slight = 1, moderate = 2 and severe = 3). Ultrapure water was also tested in the same manner at these sites on separate occasions.

Only 1 site was tested on any particular day, and several days were left between testing on the

same site to avoid any false positives being elicited. Visual skin parameters (i.e. erythema and dryness) at each of the test sites were assessed prior to application, immediately after and 24 hr after application for panellists care, to ensure that no adverse or prolonged reactions developed.

Stinger classification

The level of stinging elicited by the application of 10% lactic acid on the nasolabial fold at 2.5, 5 and 8 min for each panellist was given a numerical value as detailed above. If the sum of the responses at these time points was ≥ 2 , the panellist was classified as a stinger, and if the sum of the values was < 2 , the panellist was classified as a non-stinger.

Analysis of results

The differences between occlusion and open application were analysed, with the stinging responses at the different sites were compared using logistic regression. These analyses were also conducted separately in each case for males and females, stingers and non-stingers to establish whether the relative sensitivity of the sites was dependant on either of these factors (gender or stinging susceptibility) at any point. To compare sexes and stingers in terms of absolute sensitivity, a χ^2 test was employed. In each case, a P -value = 0.1 was considered significant. The mean responses at the different time points and the summed scores for each site were compared. Similarities between skin type and the level of stinging response at the different sites were compared using a Kruskal–Wallis test.

Results

The panellists were classified as stingers or non-stingers from their responses to the application of 10% lactic acid on the nasolabial fold according to the classification criteria outlined above. 19 panellists were classified as stingers, 5 of these being male and 14 being female; the remaining 26 panellists were classified as non-stingers, of whom 12 were male and 14 female. These proportions are similar to those previously reported (9).

Occlusion versus open application

Overall, the level of perceived subjective irritation under occlusion was very low, with only 20 of the 45 panellists participating in the study reporting any stinging response at any site under occlusion. The open application of 10% lactic acid resulted in significantly greater levels of stinging at any site than application made under occlusion. Thus,

no further analysis was conducted on the results obtained by occlusive treatment.

Male versus female

A difference between the response of males and females to the application of 10% lactic acid was noticed, as summarized in Table 1, with females showing a trend towards being more sensitive to the application of lactic acid than males. This difference was significant at 5 min (χ^2 test, $P=0.098$). There were no significant differences between the sexes in terms of the relative sensitivity of the different test sites as evidenced by a P -value of 0.59 and 0.46, respectively, (logistic regression).

Anatomical variations

The nasolabial fold and forehead gave higher levels of stinging responses than the chin and malar eminence, as indicated by the mean scores summarized in Tables 2 and 3. A difference between the reactivity of the nasolabial fold and forehead also was apparent. Application to the nasolabial fold triggered a rapid response, with stinging responses peaking at 2.5 min. In contrast, the forehead was associated with a more delayed response with reactions peaking from 5 min onwards.

33 of the 45 panellists participating in the study recorded different levels of response on the forehead and nasolabial fold, indicating that reactivity at one skin site was not always predictive of reactivity at the other site. Furthermore, a trend was seen for non-stingers to record a higher response on the forehead than the nasolabial fold. When comparing the mean responses of these 2 groups at each site, a difference was apparent for non-stingers between the nasolabial fold and forehead, with the responses on the forehead being greater than those on the nasolabial fold, as summarized in Table 4.

There were 2 panellists with type 1 skin, 9 with type 2, 21 with type 3 and 2 with type 4. Due to the small number of panellists with type 1 and type 4 skin, analysis was hampered and only those with type 2 and type 3 skin could be compared statistically. With regard to skin type, there were

Table 1. Percentage of males and females with stinging reactions > or < than the median

	2.5 min		5 min		8 min	
	>	<	>	<	>	<
Females (%)	35.7	64.3	60.7	39.3	57	43
Males (%)	17.6	82.4	35.3	64.7	35.3	64.7

Table 2. Mean responses on each test site at the 3 time points

Time point	Nasolabial fold	Forehead	Chin	Malar eminence
2.5 min	0.9	0.7	0.6	0.7
5 min	0.6	0.8	0.5	0.6
8 min	0.5	0.8	0.5	0.5

Table 3. Mean of the sum of the responses on each test site

Area	Mean of the summed values
Nasolabial fold	1.9
Forehead	2.4
Cheek	1.8
Chin	1.5

Table 4. Mean response for stingers and non-stingers

	Nasolabial fold	Forehead	Chin	Malar eminence
Stinger	3.9	3.3	2.2	2.9
Non-stinger	0.5	2.0	1.1	1.0

no positive relationships between the level of stinging response and skin type as evidenced by a P -value of 0.9814.

Other considerations

There was no relationship between the sensitivity of stingers and non-stingers in relation to their skin type; indeed, the skin type distributions were almost identical for the 2 groups (Table 5) and neither was there any clear relationship between stinging sensitivity and panellists' susceptibility to skin irritation (8) (Table 6). For the latter dataset, a Kruskal–Wallis test was applied, the resultant P -value of 0.7084 indicating that there was no relationship between irritant susceptibility and responses to 10% lactic acid on the forehead.

Discussion

It is becoming increasingly apparent that adverse subjective irritation commonly occurs and can be sufficiently problematic to deter individuals from using further even the most effective of products

Table 5. Relationship between skin type and stinging susceptibility

Skin type*	Stinger (%)	Non-stinger (%)
1	5†	7
2	25	29
3	65	57
4	5	7

*Skin type based on sunlight sensitivity.

†% of the panel with that skin type.

Table 6. Stinging/irritation correlation

	Reactivity to 48 hr patch with 0.3% aq. sodium lauryl sulfate		
	Never	Occasionally	Always
Stingers (%)	16	16	68
Non-stingers (%)	12	19	69

Table 6 displays the general pattern of reactivity to sodium lauryl sulfate treatment displayed during the preceding 2 years by the panellists in the stinging and non-stinging groups. Each panellist had participated in a few patch tests during this period.

(11, 12). This could be of particular concern where the products form a key element of an occupational skin care programme. Thus, it is important to find tests, which can identify products with a potential to cause subjective irritation before they reach the consumer. One such procedure is the sting test (5). This test is widely used in various modified forms, and many different factors have been identified as having an influence on the sensitivity of this test, including the anatomical region to which the test material is applied. The application of the test materials under occlusion has also more recently been proposed (6). Accordingly, we have investigated a number of aspects of the methodology, including differing anatomical regions of the face and a comparison of the impact of occlusion versus open application. The current work used a 4-point scale to assess itch, burn and sting. Robinson and Perkins (12) have more recently used a labelled magnitude scale which provides a continuum of intensity rankings, on which panellists rate the level of response experienced; this provides ratio-level data which allows the proportional difference in response to be determined, thus may be able to define better the differences between the test sites.

The volunteer panel for this study consisted of 45 participants, of whom 19 (42%) were classified as stingers. In this panel, the application of 10% lactic acid under occlusion failed to produce an appreciable stinging response at any site, with only 20 of the 45 panellists participating reporting any stinging response at some point during the study. Several panellists commented on the irritation experienced from the wearing of the chamber, which in itself could detract from any irritation caused by the lactic acid. Interestingly, there was little correlation between those classified as stingers (via reactions at the nasolabial fold) and those who experienced stinging under occlusion.

When sex differences were examined, a slight trend for females to be more sensitive to the application of lactic acid was observed (Table 1). This trend was statistically significant at 5 min. It

has been suggested that women are generally more sensitive and therefore more likely to develop stinging responses than men, although this difference has not been conclusively demonstrated to date (6). The data presented in this report suggest that this is true; however, when examining the members of the male proportion of the panel, only 5 of the 17 males participating were classified as stingers during the screening test. This could either be construed as evidence that males are generally less likely to be stingers or just a coincidence that the men recruited for this study represented an insensitive proportion of the population. It would be of value to test a larger group of male volunteers to elucidate whether a higher proportion of stingers can be found.

The data show that the response to 10% lactic acid on the nasolabial fold was rapid, with the peak responses occurring by 2.5 min compared with the later response seen on the forehead, where peak stinging responses transpired by the 5 min assessment (Table 2). The responses on the chin and cheek were less pronounced. It is also interesting to note that the mean stinging responses of non-stingers on the forehead, chin and cheek were greater than the mean stinging response they reported on the nasolabial fold, this data being summarized in Table 4. The differences between the levels of response on the different sites could be attributed to the regional variations in concentration of nociceptors. Non-stingers by nature of their classification have little or no response to the application of lactic acid on the nasolabial fold, thus it might be assumed that they would be unlikely to react strongly at any of the other sites. However, the data from this study suggest otherwise, with a quite noticeable response occurring on the forehead. Previously, only marginal responses have been noted when 10% lactic acid is applied to the forehead (5–7). Perhaps, this can be attributed to the fact that in previous work only small groups of stingers have been tested. In this study, non-stingers were also employed for the main body of testing and it is within this group that the higher responses on the

forehead occurred. It was not practical during this study to conduct a complete analysis of the relationship between skin type and the level of response elicited on the different site, due to the small number of panellists with skin type 1 and 4. From the limited analysis that was performed, there appears to be no positive relationship between skin type and the level of stinging response at the different sites.

In conclusion, this study demonstrates that there is no clear correlation between stinging responses on the nasolabial fold and other regions of the face. Thus, a positive stinging response on the nasolabial fold may not necessarily predict subjective responses to a product when used on other areas of the face. The sting test is a valuable tool and this study suggests that providing sufficient screening is conducted to ensure panellists are sensitive in the area to be tested, all the aforementioned regions could be utilized.

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