

Susceptibility to skin stinging, non-immunologic contact urticaria and acute skin irritation; is there a relationship?

J. COVERLY, L. PETERS, E. WHITTLE AND D. A. BASKETTER

Unilever Environmental Safety Laboratory, Sharnbrook, Bedford, UK

Adverse skin reactions cover many types of response: toxic, irritant, allergic, urticarial, sensory, etc. The relationships between an individual's tendency to develop different types of skin response are not well-described. We examined whether those who perceive stinging might be more likely to experience urticarial, sensory and irritation reactions in skin. A panel of 86 volunteers was tested with 10% lactic acid in the nasolabial fold to assess their ability to perceive stinging. At the same time, their capacity to develop non-immunologic contact urticaria was evaluated using chemicals of different structural type and urticant ability: methyl nicotinate, benzoic acid, cinnamic acid, cinnamaldehyde and dimethyl sulfoxide (DMSO). DMSO was also used to assess sensory effects and skin irritation. 44 were classed as "stingers" and 42 as "non-stingers". The pattern of urticant reactivity in the stingers and non-stingers was essentially the same, with neat DMSO generating the strongest reactions in both groups. Sensory reactions to DMSO (stinging, itching, tingling or burning) were similar in stingers and non-stingers; although the former may have reacted more quickly, a smaller proportion reacted (64% versus 76%). The skin irritation response to DMSO was also identical in stingers and non-stingers and the intensity of the urticant response in an individual did not correlate with the intensity of their subsequent irritant reaction. In conclusion, this study demonstrated that an individual's ability to perceive skin stinging does not give a general indication of their susceptibility to other types of non-immunologic skin response. Indeed, there appeared to be little evidence of correlations between any of the skin effects studied.

Key words: stingers; non-immunologic contact urticaria; acute irritant contact dermatitis; methyl nicotinate; benzoic acid; cinnamic acid; cinnamic aldehyde; dimethyl sulfoxide; visual assessment; sensitive skin. © Munksgaard, 1998.

Accepted for publication 29 September 1997

For many individuals, the adverse reactions associated with products that come into contact with the skin are not those of frank irritation or allergy. Rather, they tend to be a more subtle type of skin irritation, a transient redness, soreness or even a sensory effect usually without any obvious longer-term clinical sequelae (1–2). These types of skin reactivity are well known (3–5), but generally have not been investigated in detail in larger groups of subjects, particularly in terms of the relationship, either in an individual or within a group, between the effects. Previously, it has been suggested that there is some correlation between propensity to skin stinging and the development of irritation (6), although this could not be demonstrated by others (7, 8). In addition, it has been suggested that those most prone to experience skin stinging may also develop stronger reactions when exposed to chemicals that

cause non-immunologic contact urticaria (NICU) (7). In the present work, we chose to examine irritant, sensory and urticarial endpoints simultaneously, in a large group of human volunteers, to try to provide more definitive answers to the question of the relationship between these effects.

Materials and Methods

The study was approved by the Colworth Research Ethics Committee; all volunteers gave fully informed written consent.

Test materials

The substances used in the study were lactic acid (1.1 M (=10%) in distilled water), methyl nicotinate (5 mM in petrolatum), benzoic acid (1 M in

petrolatum), trans cinnamic acid (125 mM in petrolatum), cinnamaldehyde (125 mM in petrolatum), dimethyl sulfoxide (DMSO – used undiluted). The control material was distilled water.

Test panel

The panel comprised 86 healthy Caucasian adults (33 male and 53 female), age range 19–62 years, mean age 37.3 years. Patches were Finn Chambers on Scanpor (Epitest, Oy, Finland). Urticaria testing was carried out following the approach previously described (9). In brief, test materials suspended in petrolatum were applied directly to the disc, filter paper discs being necessary to apply DMSO. Materials were applied according to 1 of 5 random treatment site plans. The patches were applied for 20 min to the volar forearm, after which they were removed. Treatment sites were wiped immediately and assessed 10 min after patch removal. Whilst the patch was on the forearm, the sensory perception test was carried out. This involved the application (using a cotton wool bud) of 10% aqueous lactic acid to 1 nasolabial fold and distilled water to the other, broadly following the methodology described by Frosch & Kligman (5).

Assessment of reactions

Subjects completed a self-assessment questionnaire detailing their stinging responses on a simple

“none, slight, moderate, severe” scale at 2.5, 5 and 8 min post treatment. Sites on the volar forearm that had been treated with the urticants were assessed for both degree and spread of erythema 10 min after removal of the patch, according to the criteria shown in Table 1. Other assessment parameters, such as oedema, wrinkling, glazing and vesicles, were also assessed and recorded as comments by a trained assessor. Any other reaction features were recorded as assessor comments. Follow-up assessments were performed for panellist care only, results of these assessments not having been reported.

Analysis of data

During the 8 min treatment period, panellists completed the sensory perception assessment questionnaire by circling what they perceived to be the appropriate level of stinging (none, slight, moderate or severe). Panellists' stinging responses were converted to a numerical value and recorded onto a summary of stinging table.

none	(i.e., no stinging)	=0
slight	(i.e., slight stinging)	=1
moderate	(i.e., moderate stinging)	=2
severe	(i.e., severe stinging)	=3

The stinging values for the responses at 2.5, 5 and 8 min were summated for lactic acid, giving a maximum possible score of 9. If this total was ≥ 2 then they were categorised as ‘Stingers’. If the response was ≥ 5 , the individual was classed as a high responder. The mean and standard deviation were calculated for urticant-induced erythema and spread of erythema from patch test scores for “stingers” and “non-stingers”.

Data analysis

It is important to note that the visually assessed erythema scores recorded in this work are not on a cardinal scale and thus cannot be regarded in the same manner. However, simple manipulation to provide, for example, mean erythema values can nevertheless be informative. The mean erythema data were analysed using the Cochran-Mantel-Haenszel method to estimate the likelihood of there being a (linear) relationship between a stinging reaction and the intensity of the urticarial patch test reaction. The total number of comments on sensory effects and the number of panellists commenting were calculated for each type of comment made. The total number of comments made (irrespective of comment type and to which test material) and the total number of panellists commenting, were also calculated.

Table 1. Visual assessment of erythema grading scale

Grade	Erythematous reaction
0	no reaction
+	marginal reaction
1	slight perceptible erythema
1+	a greater than slight reaction, insufficient to be classed as clearly visible
2	clearly visible erythema
2+	a greater reaction, but insufficient to be classed as distinct
3	distinct, possibly spreading erythema
3+	a greater reaction which is not sufficient to be classed as strong
4	strong erythema which may extend beyond the treatment site
4+	a more intense reaction than above
5	very strong erythema which may extend beyond the treatment site
5+	a more intense reaction than above
6	intense, deep spreading rash-like erythema
6+	a more intense reaction than above

NB: Each grade of reaction is for the *whole site*, or the subsequent grade on *part* of the site, e.g., 1=perceptible erythema on the whole site or distinct erythema on part of the site. The ability of trained graders to make reliable, reproducible assessments using this type of detailed scale has been documented elsewhere (22). Spread of erythema was measured with the aid of a metric circles template.

Table 2. Number of panellists experiencing each total stinging score

		Stinging grade							
0	1	2	3	4	5	6	7	8	9
non-stingers		stingers ^{a)}							
27	15	9	12	11	6	4	1	1	0

^{a)} Individuals with ≥ 5 were regarded as high responders.

Table 3. Summary of data for erythema and spread for stingers versus non-stingers

Urticant	Stingers		Non-stingers	
	mean	SD ^{a)}	mean	SD
<i>methyl nicotinate</i>				
erythema ^{b)}	3.4/3.3 ^{c)}	1.0	3.3	1.1
spread ^{d)}	16.5	10.9	16.7	9.2
<i>benzoic acid</i>				
erythema	3.1/2.8 ^{e)}	1.4	2.4	1.5
spread	13.9	11.4	10.5	4.3
<i>trans cinnamic acid</i>				
erythema	1.5/1.2 ^{f)}	1.4	0.7	1.0
spread	10.1	8.4	8.6	1.7
<i>cinnamaldehyde</i>				
erythema	3.2/3.1	1.2	3.1	1.3
spread	15.6	11.9	11.9	4.3
<i>DMSO</i>				
erythema	3.8/3.6	0.9	3.6	0.8
spread	28.2	11.9	31.2	14.1

^{a)} Standard deviation; value for stingers refers only to the first mean erythema score.

^{b)} Mean erythema measured on a 14 point scale from 0–6 +.

^{c)} Values for all stingers/high responders.

^{d)} Spread diameter measured in mm.

^{e)} Significantly greater value than in non-stingers ($p=0.021$).

^{f)} Significantly greater value than in non-stingers ($p=0.003$).

Results

The details of the 86 volunteers ability to experience a stinging response to lactic acid are shown in Table 2. 42 subjects (23 female, 19 male; mean age 37.3 years) were graded as non-stingers, whilst 44 individuals (30 female, 14 male; mean age 37.4 years) were classed as stingers, of whom 12 could be regarded as high responders since they recorded a score of ≥ 5 on the arbitrary scale of 0–9.

The mean intensity and spread of erythema for the 5 urticants is given in Table 3. At the concen-

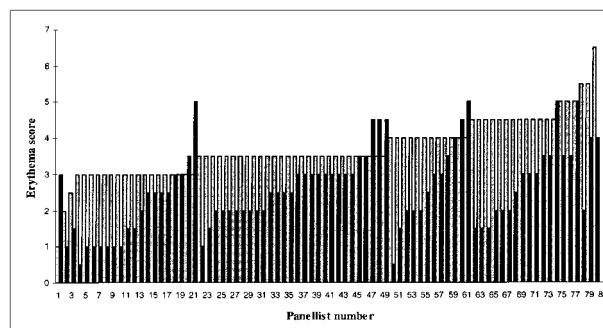


Fig. 1. The bar chart shows individual comparisons of reactivity for all panellists who completed scoring of their DMSO erythema reactions at 30 min (pale bars) and 24 h (dark bars). Erythema grades were sorted according to intensity, firstly for urticaria, then for irritation.

trations used, the order of urticant reactivity judged by both intensity and/or spread of erythema was the same for stingers and non-stingers: DMSO > methyl nicotinate > cinnamaldehyde > benzoic acid > trans cinnamic acid. As reported previously, a high reactivity to one urticant was not predictive of high reactivity to the other urticants (10): for the sake of brevity, the analytical details are not repeated here. It was evident that for 3 of the urticants (methyl nicotinate, cinnamic aldehyde and DMSO) there was no difference in the response of stingers and non-stingers. In contrast, for benzoic acid and trans cinnamic acid, both the mean intensity of erythema and its spread were greater in the panellists graded as stingers. The differences in erythema were significant according to the Cochran-Mantel-Haenszel statistic. However, analysis of the data in terms of the sub-group of those who were particularly sensitive in the lactic acid stinging test (12 subjects in all) did not indicate they were even more reactive to these 2 urticants. In fact, their mean erythema values were virtually identical to those of the larger group of stingers (Table 3). Other skin responses to the urticants were minor in comparison to the erythema and did not affect the conclusions (data not shown).

As DMSO is not only a cause of non-immunologic contact urticaria but also of skin irritation and sensory effects, we were able to investigate

Table 4. Pattern of sensory, urticant and irritant responses to DMSO

Category	% panel with sensory reaction	Slight sensory reactions	Moderate sensory reactions	Severe sensory reactions	Mean urticarial reaction	Mean irritation reaction
stingers	64%	3S, 2I, 2B ^{a)}	9S, 5I, 2B	2S, 2I, 1B	3.8	2.6
non-stingers	76%	2S, 6I, 2B	5S, 9I, 3B	4S, 1I	3.6	2.5

^{a)} Number of responses to DMSO: S=stinging; I=itching; B=burning. Note that not all panellists reported a skin sensory reaction.

Table 5. Sex variation in response to urticants

Sex	Methyl nicotinate	Benzoic acid	Trans cinnamic acid	Cinnamaldehyde	DMSO
female	3.6/3.3 ^{a)}	3.3/2.3	1.2/0.4	3.4/2.6	3.9/3.7
male	3.4/3.4	2.6/2.5	2.1/1.1	3.3/3.4	3.7/3.5
both	3.5/3.3	3.1/2.4	1.5/0.7	3.4/2.9	3.8/3.6

^{a)} Mean erythema values for stingers/non-stingers.

whether there was any relationship between skin stinging, sensory effects, urticaria and irritation in this large group of subjects. A summary of the results is provided in Table 4. There was no real difference in the number or type of sensory reactions in stingers and non-stingers, although non-stingers had rather more slight/moderate responses, especially of the "itch" type. The urticarial and irritation responses to DMSO were identical in stingers and non-stingers. Interestingly, if the whole group was categorized according to the intensity of their urticant reactivity to DMSO, the irritant responses in an individual appeared to bear no relationship to the intensity of their preceding urticarial reaction (Fig. 1).

There was very little effect of the sex of the individual on the response to the urticants, in either the stinging or the non-stinging group (Table 5). However, it was noticeable that in the case of trans-cinnamic acid, in both of these groups the mean erythema score in women was much lower than in the men. The trend to a lower response to trans cinnamic acid occurred in both male and female non-stingers. For benzoic acid, much of the significantly higher response in stingers noted in Table 3 appeared actually to be due to the greater reactivity in women (Table 5). The difference in responses of male stingers and non-stingers to benzoic acid was not statistically significant.

Conclusions

Adverse skin reactions cover a wide range of effects, from immediate toxic effects such as corrosion (11) to the most minor sensory effects (1–2). This span is probably more than matched by the heterogeneity in the reactivity of individuals; for example a dose of an irritant that failed to induce any reaction in 99 British individuals caused a clear response in the 100th (12); in another study of non-immunologic contact urticaria, 197 German volunteers reacted to 1 or more of the urticants, many strongly, but 3 subjects completely failed to respond at all (10).

It is interesting to try to understand what determines the propensity of an individual to react to a specific stimulus, but it is also worthwhile to enquire into the relationships between the different

types of skin response. A particular driving force behind such an investigation is our wish to understand how we may be able to use small carefully selected groups of individuals to assist in the determination of the skin compatibility of materials which will come into contact with the skin (13–15). Such investigations also may be germane to the matter of "sensitive skin" (16) and "status cosmeticus" (17). At present, the published literature on the relationship between such non-immunologic skin reactions as stinging, urticaria and irritation is relatively limited and tends to suggest that correlations between these reactivities are at best weak. For example, Lammintausta et al. (7) studied 74 females to investigate relationships between susceptibility to skin stinging, urticaria and irritation. This work found that stingers generally were not more likely to experience sodium lauryl sulfate (SLS) induced irritation, but did react more strongly to the urticants benzoic acid and sorbic acid. However, their panel of stingers numbered only 8. Others have shown in a larger panel (8) that propensity to stinging did not correlate with susceptibility to SLS-induced acute skin irritation. Furthermore, it is quite clear that strong reactivity to one non-immunologic urticant is not necessarily predictive of the degree of response to other such urticants (13).

Combining these pieces of information, it seems unlikely that susceptibility to lactic acid stinging would correlate generally with urticant susceptibility. Consequently, we chose to assess reactivity to a range of urticants, in the belief that these would not all operate by the same mechanism, and thus it might be predicted that some of them would give greater responses in stingers, whilst others would not. The results presented herein confirm that the urticarial response to benzoic acid is greater in stingers, as was earlier reported (7). The effect was not great, but was significant ($p=0.021$) due to the large panel sizes; somewhat surprisingly, the difference was not enhanced when the particularly sensitive group (of stingers) was separated out. However, it was quite noticeable that the reduction of the benzoic acid urticaria was more pronounced in female compared to male stingers (Table 5). The urticarial response to trans cinnamic acid was also higher in stingers, but again, and somewhat surprisingly, this was not more obvious in the high responder group.

In contrast to the above, the level of reactivity to all the other urticants was essentially identical in stingers (even the highly sensitive) and non-stingers and in males and females. Perhaps this finding suggests that urticaria from cinnamaldehyde, methyl nicotinate and DMSO involves different mechanisms to benzoic acid and trans cinnamic acid. In

support of this, it is interesting that whilst cinnamaldehyde, methyl nicotinate and DMSO all produce an immediate erythema in guinea pig skin, benzoic acid and trans cinnamic acid do not (18). Similarly, there are differences in the ability of these chemicals to induce ear swelling (reviewed in 19).

It is particularly noteworthy that those who were classified as stingers, on average gave very similar urticant, irritant and sensory responses to the 20 min occluded application of DMSO. Thus, at least with this one substance, there does not appear to be a general trend; greater reactivity to one of the parameters does not suggest likely greater reactivity to the other endpoints. Further support for the differentiation of the various types of non-immunologic skin responses can be derived from the attempts to use "quick tests" to predict susceptibility to acute irritation, which have not succeeded (20), the authors suggesting that different pathophysiological pathways could be involved. Whilst some workers have identified apparent correlations between certain of the endpoints discussed in the present paper (6, 7), others have not been able to confirm these findings (8, 13). Part of the reason for this may lie in panellist selection and in certain cases the relatively small number of panellists used. In the present work, all of the panellists were normal healthy volunteers; the group sizes were comparatively large. In the present work, we elected not to use bioengineering techniques, not only for practical reasons, but particularly because the study design meant that we were well on scale with visual assessment. The manner in which we carry out visual assessment with specially trained observers means that reliable, high quality data, in which subtle low grades of erythema can be distinguished, is obtained (21).

In conclusion, the results presented indicate that the patterns of skin reactivity, stinging, other sensory effects, urticaria and irritation are not phenomena that are closely correlated. Neither do these effects correlate well with the sex of the individual. Consequently, the definition of "sensitive panels" needs to be approached with great caution; we find it difficult to endorse the generalization that stingers represent a "subpopulation with a more general tendency to have skin reactions" (22).

Acknowledgements

The authors thank Matt Rowson for his expert assistance with the statistical analyses.

References

1. Frosch P J, Kligman A M. Recognition of chemically vulnerable and delicate skin. In: *Principles of cosmetics for the dermatologist*. St Louis: Mosby, 1982: 287–296.

2. Amin S, Maibach H I. Cosmetic intolerance syndrome: pathophysiology and management. *Cosmet Toilet* 1996; 107: 34–42.
3. Maes D, Marenus K, Smith W P. Invisible irritation: a new look at product safety. *Cosmet Toilet* 1990; 105: 43–50.
4. Odom R B, Maibach H I. Contact urticaria. A different contact dermatitis. *Cutis* 1976; 18: 672–676.
5. Frosch P J, Kligman A M. A method for appraising the stinging capacity of topically applied substances. *Journal of Cosmetic Chemistry* 1977; 28: 197–209.
6. Soschin D, Kligman A M. Adverse subjective responses. In: *Safety and efficacy of topical drugs and cosmetics*. New York: Grune and Stratton, 1982: 377–388.
7. Lammintausta K, Maibach H I, Wilson D. Mechanisms of subjective (sensory) irritation. Propensity to non-immunologic contact urticaria and objective irritation in stingers. *Dermatosen* 1988; 36: 45–49.
8. Basketter D A, Griffiths H A. A study of the relationship between susceptibility to skin stinging and skin irritation. *Contact Dermatitis* 1993; 29: 185–188.
9. Safford R J, Allenby C F, Basketter D A, Goodwin B F J. Immediate reactions to fragrance chemicals and a study of factors influencing contact urticaria to cinnamic aldehyde in humans and guinea pigs. *British Journal of Dermatology* 1990; 123: 595–606.
10. Basketter D A, Wilhelm K P. Studies on non-immune contact reactions in an unselected population. *Contact Dermatitis* 1996; 35: 237–240.
11. Holland G, York M, Basketter D A. Irritants: corrosive materials, oxidising/reducing agents, acids and alkalis, concentrated salt solutions etc. In: Maibach H I, Coenraads P J (eds): *Irritant contact dermatitis syndrome*. Boca Raton, FL, USA: CRC Press, 55–64.
12. Basketter D A, Griffiths H A, Wang X M, Wilhelm K-P, McFadden J. Individual, ethnic and seasonal variability in irritant susceptibility of skin: the implications for a predictive human patch test. *Contact Dermatitis* 1996; 35: 208–213.
13. Jenkins H L, Adams M G. Progressive evaluation of skin irritancy of cosmetics using human volunteers. *International Journal of Cosmetic Science* 1989; 11: 141–149.
14. Walker A P, Basketter D A, Baverel M, Diembeck W, Matthies W, Mougins D, Paye M, Rothlisburger R, Dupuis J. Test guideline for assessment of skin compatibility of cosmetic finished products in man. *Food and Chem Toxicol* 1996; 34: 551–560.
15. Walker A P, Basketter D A, Baverel M, Diembeck W, Matthies W, Mougins D, Paye M, Rothlisburger R, Dupuis J. Test guidelines for assessment of skin tolerance of potentially irritant cosmetic ingredients in man. *Food and Chem Toxicol* 1997; in press.
16. Draeos Z D. Sensitive skin: perceptions, evaluation and treatment. *American Journal of Contact Dermatitis* 1997; 8: 67–78.
17. Fisher A A. Cosmetic actions and reactions: therapeutic, irritant and allergic. *Cutis* 1980; 26: 22–29.
18. Lahti A. Non-immunologic contact urticaria. Animal tests and their relevance. *Acta Dermato-venereologica* 1988; 68: 43–44.
19. Amin S, Lahti A, Maibach H I. Contact urticaria and the contact urticaria syndrome (immediate contact reactions). In: *Dermatotoxicology* 1995: 485–503.
20. Bangha E, Hinnen U, Elsner P. Irritancy testing in occupational dermatology: Comparison between two quick tests and the acute irritation induced by sodium lauryl sulphate. *Acta Dermato-venereologica* 1996; 76: 450–452.
21. Basketter D A, Reynolds F S, Rowson M, Talbot C, Whittle E. Visual assessment of human skin irritation: a sensitive and reproducible tool. *Contact Dermatitis* 1997; 37: 218–220.

22. Issachar N, Gall Y, Borell M T, Poelman M-C. pH measurements during lactic acid stinging test in normal and sensitive skin. *Contact Dermatitis* 1997; 36: 152–155.

Address:

*D. A. Basketter
Unilever Environmental Safety Laboratory
Colworth House, Sharnbrook
Bedford, MK44 1LQ
UK*