

Allergy to ingredients of vehicles

MATTI HANNUKSELA, MERJA KOUSA AND VEIKKO PIRILÄ

Department of Dermatology, University Central Hospital, Helsinki, Finland

Common ingredients of vehicles such as perfumes, antibacterial agents, emulsifiers and other surface active agents, propylene glycol, lanolin and wool alcohols were tested in eczema patients over a three-year period. Perfume allergy was detected in 3.6 % of the cases, sensitivity to thiomersal in 2 %, to sorbic acid in 0.8 %, to parabens in only 0.3 %, and to wool alcohols in 1.2 %. Reactions to emulsifiers were seen in over 1 % of those tested.

Key words: dermatitis, contact (etiology) – ointment bases – pharmaceutical aids.

Received for publication October 10, 1975

Hypersensitivity to the ingredients of vehicles may be manifest only as itching and slight redness on the treated area. However, severe eczemas are sometimes seen. The testing of vehicles as such is often fruitless because the concentrations of the various ingredients may be so low that epicutaneous tests on healthy skin remain negative. In addition, steroids in ointments may have an influence on test reactions.

Classical ointment bases with petrolatum and mineral oils are usually harmless. Cream bases contain at least preservatives and emulsifiers but usually also antioxidants, lanolin or wool alcohols and perfumes as possible allergens. Synthetic vehicles containing polyethylene glycols, propylene glycol and/or fatty alcohols may also be sensitizers.

This study is a three-year survey of tests with various ingredients of vehicles used externally.

Patients and Methods

All the patients included in the series were suffering from eczema and were suspected

of having contact sensitivities. The distribution according to age and sex is given in Table 1. The epicutaneous tests were made using the chamber method described by Pirilä (1975) on the backs of the patients. The tests were removed after 20–24 hours and read for the first time about 30 minutes after removing the tests, and subsequently on the second day and on the fourth or fifth day after the application of the tests. The test substances mentioned in this study were incorporated in petrolatum with the exception of formaldehyde (in water) and propylene glycol (in water).

Results

1. *Perfumes*

Balsam of Peru was used as the only screening test for perfume allergy for the first 1 ½ years. In addition, perfumes of various cosmetics were tested separately. Usually one out of four patients with an allergic reaction to the Peruvian balsam also reacted to the perfumes. By chance we found that the perfume of an aftershave lotion gave positive results nearly as often as the balsam

Table 1. Total clinical material (4,097 patients).

Age years	≤15	16-25	26-35	36-45	46-55	56+
%	4	18	18	15	16	29
Females	61 %					
Males	39 %					

(Table 2). Since then, we have used this perfume as an additional fragrance screening test. Balsam of Peru and the screening test perfume showed cross-reactivity in 44% of the cases. Cross-reactions between them and colophony and wood tars were rarer (Table 3).

Components of the Peruvian balsam were not tested separately. In one case, the sensitizer underlying a very acute perfume dermatitis was detected. This particular patient, a 34-year-old man, had noticed that an aftershave lotion caused redness and itching within a few hours. Once, after the patient had had his hair cut, the barber applied the same lotion to the patient's neck.

Within four hours, a very acute eczema appeared, which reached its maximum in 24 hours. Epicutaneous tests with the components of the perfume (kindly supplied by the manufacturer) revealed that the only component causing reaction was "Mousse de Chêne". Another patient, an 18-year-old boy, also complained of itching and dermatitis after using the same lotion. In this case, isoeugenol gave the strongest reaction and was probably the sensitizer.

2. Antibacterial agents, preservatives and antioxidants

Thiomersal proved to be the most common allergen in this group. In the whole series, 2 % demonstrated allergic reactions (Table 2). This sensitivity was more common in patients under 35 years of age (4.4 %) than among older patients (0.3 %).

Reactions to sorbic acid were recorded in 0.8 % of cases, but parabens seem to be rare sensitizers in Finland (Table 2). Hexachlorophene tested at 1 % in petrolatum and Irgasan DP 300® (1 % in petrolatum)

Table 2. Allergic reactions to ingredients of vehicles.

Substance	Concentration %	Tested No.	Positive No.	Positive %
Balsam of Peru	25.0	4,097	177	4.3
Perfume	3.0	1,823	66	3.6
Thiomersal	0.1	1,823	37	2.0
Formaldehyde	2.0	3,041	54	1.8
Wool alcohols	30.0	2,538	31	1.2
Lanolin	as is	2,538	14	0.6
Lanette N	20.0	486	7	1.4
Sorbic acid	2.5	606	5	0.8
Atlas G 2162®	20.0	486	4	0.8
Atlas G 1441®	20.0	412	2	0.5
Arlacel 83®	20.0	486	2	0.4
Span 60® + 80®	5.0 + 5.0	486	2	0.4
Parabens	15.0	4,097	14	0.3
Hexachlorophene	1.0	1,796	6	0.3
Triethanolaminestearate	5.0	412	1	0.2
Tween 40® + 80®	5.0 + 5.0	412	1	0.2
Propylene glycol	2.0	880	2	0.2
Irgasan DP 300®	1.0	1,796	1	0.1

elicited positive reactions in only 0.3 and 0.1 % of the cases respectively. Other antimicrobial agents were tested only in selected patients; positive results were found in 1 to 4 cases with each agent (Table 4). In addition, butylhydroxytoluene and lauryl gallate were tested in 78 cases with negative results.

3. Surface active agents (including emulsifiers)

Emulsifiers were added to our routine test series in January 1975. Within a few months, several allergic reactions were seen. Among the seven emulsifiers tested, Lanette N was found to be the most common allergen, and even Tweens and Spans caused reactions in one and two cases respectively (Table 2).

Of the cationic surface active agents, benzalkonium chloride and benzethonium chloride, and of the non-ionic ones, lauric and myristic acid dialkanolamide were found to be allergens in 1 to 4 cases (Table 4).

4. Miscellaneous

Reactions to wool alcohols were encountered

Table 4. Allergic reactions to ingredients of vehicles which were not routinely tested.

Antimicrobial agents and antioxidants

		No. of cases
Chlorhexidine	1 %	4
Triclocarban	5 %	3
Ethylenediamine	0.1 %	3
Chloracetamide	0.5 %	1
Chlorbutanol	5 %	1
Chlorocresol	2 %	1
Thonzonium bromide	2 %	1
Tocopherol d-1- α	10 %	1
Cloflucarban	1 %	1

Surface active agents

Cationic

Benzalkonium chloride	0.1 %	4
Benzethonium chloride	0.5 %	1

Nonionic

Lauryl and myristic acid dialkanolamide	1 %	1
---	-----	---

ed in 1.2 % and to lanolin (as is) in 0.6 % of 2,126 cases (Table 2). Hypersensitivity to formaldehyde was found in 1.8 % of those tested. The isotonic concentration of propylene glycol (2 % in water) caused positive reactions in 0.2 % of the cases.

Table 3. Cross-reactions between balsam of Peru, perfume, colophony and wood tars.

A. 102 patients allergic to balsam of Peru

Substance	Positive No.	Positive %
Perfume	44	44
Colophony	17	17
Wood tars	21	21

B. 67 patients allergic to perfume

Substance	Positive No.	Positive %
Balsam of Peru	29	43
Colophony	9	13
Wood tars	7	10

Discussion

The difficulty of developing "hypoallergenic" products is a burning question, particularly in the cosmetic industry. Perfume allergy is perhaps the most serious, especially because of the paucity of appropriate screening tests. Balsam of Peru has been widely used for this purpose. The number of positive reactions has varied greatly from one study to another, e.g. from 1.4 % to 12.2 % in the following investigations: Angelini et al. (1975), Bandmann et al. (1972), Ebner et al. (1971), Ebner (1974), Hjorth (1961), Lehmuskallio et al. (1973), Meneghini et al. (1971). In a selected series of

patients with leg ulcers. Malten et al. (1973) found patch test reactions to this balsam in 20 out of their 100 cases.

In the present study, 4.3 % of the cases reacted positively to balsam of Peru. Only half of them showed positive test results to various perfumes. The finding is in agreement with those of Hjorth (1961) and Ebner (1964). Efforts to develop fragrance test series have been made in Japan and in the USA (Larsen 1975). It will be interesting to see how these screening test series work. So far, we have been very satisfied with the perfume of a commercial aftershave lotion. In fact, we have not seen a single patient with a negative result to this particular perfume and a positive result to some other perfume(s).

The problem of paraben allergy is apparently less important in Finland than in other European countries and the USA. Bandmann and his co-workers (1972) published a multicentre study in which 1.3 % of males and 2.3 % of females were found to be allergic to parabens. In the study of Hjorth and Trolle-Lassen (1964), the number was 1.1 %, and in that of Brun (1975) 1.7 %. Only 0.3 % of our 4,097 patients reacted positively to parabens. Sorbic acid allergy seems to be more frequent (0.8 %), but the number of cases examined is still so low (606 patients) that definite conclusions cannot be drawn.

The sensitizing capacity of thiomersal has been known for some decades (Ellis 1947, Gaul 1958, Hanson & Möller 1971, Underwood et al. 1946). In Finland, this organic mercury compound is used especially as the preservative of vaccines. Nearly all people under 35 years of age have been inoculated at least against tetanus but also against pertussis and diphtheria. It seems probable that thiomersal in these vaccines is the cause of the high number of thiomersal allergies.

Hexachlorophene is a weak sensitizer, and so apparently is Irgasan DP 300®. In

addition to these antibacterial agents, chlorhexidine is commonly used as an ingredient of vehicles in Finland. Unfortunately, it was not included in the routine test series.

Sensitivity to emulsifiers and other surface active agents has not been systematically examined before. Lanette O and Lanette N (Hjorth & Trolle-Lassen 1964, Bandmann & Dohn 1967) and Tween 80® (Meneghini et al. 1971) have been found to cause reactions only in sporadic cases. On the other hand, triethanolamine allergy is relatively common (0.9–2.0 %) according to the literature (Angelini et al. 1975, Fisher et al. 1971, Meneghini et al. 1971). On the basis of the present results, allergy to emulsifiers is more common than to preservatives. It therefore seems reasonable to continue testing with common emulsifiers.

Quaternary ammonium compounds are well-known sensitizers (Fisher & Stillman 1971, Wahlberg 1962). Out of our four patients allergic to benzalkonium, two had used hair dressings with 1 % benzalkonium as an ingredient.

Wool alcohols as the sensitizer in lanolin were also noted in this study. Researches from both Europe and other parts of the world have stressed the usefulness of testing with wool alcohols to detect lanolin allergy (Bandmann et al. 1972, Epstein 1972, Fisher et al. 1971, Hjorth & Trolle-Lassen 1964, Sugai & Higashi 1975).

Formaldehyde as such is seldom, if ever, an ingredient of vehicles. However, various amounts of formaldehyde have been detected in tubes as a result of the degradation of synthetic resins used as inner coating of the tubes (Tegner 1975).

Propylene glycol is hypertonic in concentrations of over 2 % in water. Irritant reactions are frequent when tested in hypertonic concentrations under occlusion (Warsaw & Herrmann 1952, Hannuksela et al. 1975). In the latter study, true allergy was shown in 4 out of 1,556 patients. The pre-

sent results are in accordance with the previous ones.

Conclusion

Allergic reactions to the ingredients of vehicles are frequently seen in Finland. The differences between the present results and those from other European countries and the USA are the rarity of paraben allergy and the unexpectedly high number of reactions to emulsifiers and sorbic acid.

Acknowledgement

This study was supported by a grant from Schering Corp., USA.

Non-proprietary names

- Arlacel 83® = Sorbitan sesquioleate
- Atlas G 1441® = Polyoxyethylene sorbitol lanolin derivative
- Atlas G 2162® = Polyoxyethylene oxypropylene stearate
- Irgasan DP 300® = 2,4,4'-trichloro-2'-hydroxydiphenyl ether
- Span 60® = Sorbitan monostearate
- Span 80® = Sorbitan mono-oleate
- Tween 40® = Polyoxyethylene sorbitan monopalmitate
- Tween 80® = Polyoxyethylene sorbitan mono-oleate

References

- Angelini, G., Rantuccio, F. & Meneghini, C. L. (1975) Contact dermatitis in patients with leg ulcers. *Contact Dermatitis* 1, 81-87.
- Bandmann, H.-J. & Dohn, W. (1967) *Die Epicutantestung*. Munich: J. F. Bergmann.
- Bandmann, H.-J., Calnan, C. D., Cronin, E., Fregert, S., Hjorth, N., Magnusson, B., Maibach, H., Malten, K., Meneghini, C., Pirilä, V. & Wilkinson, D. (1972) Dermatitis from applied medicaments. *Archives of Dermatology* 106, 335-337.
- Brun, R. (1975) Epidemiology of contact dermatitis in Geneva (100 cases). *Contact Dermatitis* 1, 214-217.
- Ebner, H. (1974) Peru balsam und Parfüms. Untersuchungen über allergologische Beziehungen zwischen diesen Substanzen. *Der Hautarzt* 25, 123-126.
- Ebner, H. & Stöger, H. (1971) Das sogenannte "Hausfrauenekzem". *Wiener Klinische Wochenschrift* 83, 901-905.
- Ellis, F. (1947) The sensitizing factor in merthiolate. *Journal of Allergy* 18, 212-213.
- Epstein, E. (1972) The detection of lanolin allergy. *Archives of Dermatology* 106, 678-681.
- Fischer, A. A. & Stillman, M. (1971) Allergic contact sensitivity to benzalkonium chloride. *Archives of Dermatology* 106, 169-171.
- Fischer, A. A., Pascher, F. & Kanof, N. B. (1971) Allergic contact dermatitis due to ingredients of vehicles. *Archives of Dermatology* 104, 286-290.
- Gaul, E. (1958) Sensitizing component in thio-salicylic acid. *The Journal of Investigative Dermatology* 31, 91-92.
- Hannuksela, M., Pirilä, V. & Salo, O. P. (1975) Skin reactions to propylene glycol. *Contact Dermatitis* 1, 112-116.
- Hansson, H. & Möller, H. (1971) Intracutaneous test reactions to tuberculin containing merthiolate as a preservative. *Scandinavian Journal of Infectious Diseases* 3, 169-172.
- Hjorth, N. (1961) Eczematous allergy to balsams. *Acta dermatovenereologica* 46, Suppl. 211.
- Hjorth, N., Trolle-Lassen, C. (1964) Skin reactions to ointment bases. *Transactions of the St. John's Hospital Dermatological Society* 49, 127-140.
- Larsen, W. G. (1975) Cosmetic dermatitis due to a perfume. *Contact Dermatitis* 1, 142-145.
- Lehmuskallio, E., Pirilä, V. & Salo, O. P. (1973) Ulkoiset lääkeaineet kosketusallergian aiheuttajina. *Suomen Lääkärilehti* 28, 1103-1105.
- Malten, K. E., Kuiper, J. P. & Van der Staak, W. B. (1973) Contact allergic investigations in 100 patients with ulcer cruris. *Dermatologica* 147, 241-254.
- Meneghini, C. L., Rantuccio, F. & Lomuto, M. (1971) Additives, vehicles and active drugs of topical medicaments as causes of delayed-type allergic dermatitis. *Dermatologica* 143, 137-147.
- Pirilä, V. (1975) Chamber test versus patch test for epicutaneous testing. *Contact Dermatitis* 1, 48-52.
- Sugai, T. & Higashi, J. (1975) Hypersensitivity

- to hydrogenated lanolin. *Contact Dermatitis* 1, 146-157.
- Tegner, E. (1975) Personal communication.
- Underwood, G. B., Gaul, L. E., Collis, E. & Morsby, M. (1946) Overtreatment dermatitis of the feet. *The Journal of the American Medical Association* 130, 249-256.
- Wahlberg, J. E. (1962) Two cases of hypersensitivity to quaternary ammonium compounds. *Acta dermatovenereologica* 42, 230-234.
- Warsaw, T. G. & Herrmann, F. (1952) Studies of skin reactions to propylene glycol. *Journal of Investigative Dermatology* 19, 423-430.

Address:

Matti Hannuksela, M. D.
Department of Dermatology
University Central Hospital
Snellmaninkatu 14
SF-00170 Helsinki 17
Finland

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.