

ORIGINAL ARTICLE

Use of sorbitan sesquioleate in patch test preparations and patch testing with the substance—What do our results mean?

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Abstract

Background: Sorbitan sesquioleate (SSO) is a sorbitan fatty acid ester, an emulsifier used in topical products and certain patch test preparations. SSO may affect the patch test results. It has been debated whether to include the substance in the baseline series to avoid misinterpretation of the results.

Objectives: To report the prevalence and simultaneous reactions of SSO with other patch test preparations containing SSO as an emulsifier.

Materials and Methods: A retrospective analysis of 3539 dermatitis patients who underwent patch testing from 2016 to 2020 was performed.

Results: The 5-year SSO contact allergy prevalence was 0.48%, and 1.3% had a doubtful reaction. Patients with a stronger positive reaction (2+, 3+) were more likely to react simultaneously to other allergen preparations containing SSO (p value = 0.018). One patient with a strong reaction to SSO reacted positively to all SSO-containing patch test preparations. Definite fragrance allergens could not be identified in the patients who had simultaneous reactions to SSO and fragrance mix (FM) I.

Conclusions: Patch testing with allergen preparations containing SSO affected the patch test interpretation. Fragrance contact allergy could not be ruled out when a patient simultaneously reacted to SSO and FM I. Changing emulsifiers in patch test preparations would be advantageous.

KEYWORDS

2-hydroxyethyl methacrylate, atopic dermatitis, decyl glucoside, emulsifier, *Evernia prunastri* (oakmoss) extract, fragrance contact allergy, fragrance mix, *Myroxylon pereirae* resin, patch test preparations, sorbitan sesquioleate

INTRODUCTION

Sorbitan sesquioleate (SSO) is one of the sorbitan fatty acid esters commonly used in cosmetic products and topical medical preparations such as topical corticosteroids.^{1–3} It was shown to cause contact allergy, mainly reported in leg ulcer patients.⁴ It is also a common

emulsifier mixed in some patch test preparations, not only those containing multiple allergens such as fragrance mix (FM) I 8% in petrolatum (pet.) and *Myroxylon pereirae* resin (BOP) 25% in pet., but also in test preparations with discrete sensitizers with various SSO concentrations from different manufacturers (Table 1).⁵ Patch test with preparations containing SSO was brought into consideration three

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decades ago because a positive patch test reaction caused by SSO in the test preparation might be incorrectly diagnosed as a reaction to the allergen named on the test preparation. SSO may enhance both allergic and irritant patch test reactions and give divergent patch test results, especially when patch testing the patients with FM I and its constituents.⁶

Although a patch test preparation with SSO 20% in pet. is known to be beneficial in patients with leg ulcers or suspected contact allergy to cosmetics,³ it has still been globally debated whether to include it in the baseline series and whether SSO should be tested simultaneously with the constituents of FM I.^{5–10} To our knowledge, only the American Core Series by the American Contact Dermatitis Society and the German baseline series by the German Contact Dermatitis Research Group (DKG) contain SSO for screening.^{11–13}

Diagnosing contact allergy is challenging when patients have a positive reaction to SSO simultaneously with other mixed allergens containing SSO. We found that SSO interfered with interpreting the results in our fragrance study.¹⁴ Therefore, this study aimed to report the prevalence of SSO sensitisation in consecutive dermatitis patients and concomitant patch test reactions to fragrance and non-fragrance test preparations containing SSO to consider whether SSO would be useful for patch testing in various circumstances.

MATERIALS AND METHODS

Patients and patch testing

This study is a part of the fragrance contact allergy project at the Department of Occupational and Environmental Dermatology, Malmö, Faculty of Medicine, Lund University, Sweden. We retrospectively analysed the data of 3539 dermatitis patients referred for patch testing during 2016–2020. Demographic data of the patients, including age, gender, and a history of atopic dermatitis (AD, having childhood eczema diagnosed with AD), were collected. Patient inclusion, allergens, patch test procedures and readings at the clinic were conducted according to the recommended guidelines of the International Contact Dermatitis Research Group (ICDRG)¹⁵ and the European Society for Contact Dermatitis,¹⁶ described in published studies.^{14,17} Patch test reading was performed on Day (D) 3 or 4, and D7. The intensity of the reaction was read as negative, doubtful, weakly positive (1+), strongly positive (2+), extremely positive (3+) and irritant.

Concerning SSO, the allergen at the concentration of 20% in pet. had been situated in our extended baseline series, used for patch testing in every consecutive dermatitis patient. Individual FM I constituents used for patch testing were previously described.¹⁴ Fragrance test preparations that contain 5% SSO as an emulsifier at our clinic were BOP, FM I and oakmoss extract.¹² Decyl glucoside 5% in pet. and HEMA 2% in pet., which contain 5% SSO were introduced into our extended baseline series in 2019 and had not been tested in all patients in this study. All mentioned allergens were purchased from Chemotechnique MB Diagnostics AB.

Statistical analysis

Numbers and percentages of clinical data and prevalences of positive reactions to allergens are reported using descriptive analysis. The 1+, 2+ and 3+ positive reactions were grouped as positive reactions. The proportion of patients with different intensities of positive reactions to SSO (1+ vs. 2+/3+) between (i) patients with and without a history of AD and (ii) patients with and without simultaneous positive reactions to either FMI, BOP or oakmoss extract, were compared using a two-sided Fisher's exact test. The same method was used to compare the proportion of doubtful and negative reactions in AD and non-AD patients. *p* Values less than 0.05 were interpreted as having a significant statistical difference. PASW Statistics (version 23.0; SPSS Inc.) was used for the statistical analysis. This study was approved by The Swedish Ethical Review Authority (number 2020-02190).

RESULTS

Of all 3539 tested patients, 68.8% were female, and 31.2% were male. About one fourth (27.6%) of the patients had a history of AD. A positive patch test reaction to SSO was diagnosed in 17 patients (12 females and 5 males), which gave the 5-year SSO contact allergy prevalence of 0.48% (95% confidence interval = 0.3%–0.8%). The mean age $\pm$ standard deviation of patients with a positive reaction to SSO was 43.4 ± 15.4 years. Seven SSO-positive patients (41.2%) had a history of AD. Almost all (16 out of 17, 94.1%) patients reacted positively to SSO on the first reading day.

Doubtful reactions were reported in 46 patients (1.3%), of which 21 (45.7%) had a history of AD. AD patients were more likely to react doubtfully to SSO (*p* value = 0.006; 21 doubtful vs. 969 negative AD patients, and 25 doubtful vs. 2553 negative non-AD patients). Only two patients had an irritant reaction, and both had a history of AD.

Table 2 shows the demographics, patch test results and clinical relevance of 17 patients with a positive reaction to SSO. AD patients showed more frequently weak patch test reactions (1+) than strong and extreme reactions (2+, 3+) (*p* value = 0.018). Simultaneous positive reactions to SSO and any of the mixes (FM I, BOP and oakmoss extract) were more common in the patients with strong or extreme patch test reactions than in those with weak reactions to SSO (*p* value = 0.018).

Of all patients, 221, 250 and 77 had a positive reaction to FM I, BOP and oakmoss extract, respectively. Detailed information about these patients was reported.¹⁴ Regarding patients with contact allergy to FM I, the proportion of patients with concomitant positive reactions to SSO and FM I was 3.2%, whereas 4.0% and 10.4% of the patients with positive reactions to BOP and oakmoss extract had a concomitant reaction to SSO (Table 2). Patients no. 8 and 9 reacted positively only to BOP and were negative to FM I and the fragrance ingredients of the mix. Patients no. 10–17 had a positive reaction to oakmoss extract but not to other FM I ingredients. Patient no. 17 reacted positively to all allergens containing SSO in our baseline and extended baseline series, not only to FM I, BOP, and oakmoss

	SSO	Allergen, concentration and vehicle	Manufacturer
1	5%	Ethyleneurea, melamine formaldehyde mix, 5.0% pet	CD
2		<i>Evernia furfuracea</i> (tree moss) extract, 1.0% pet	SP
3		<i>Evernia prunastri</i> (oakmoss) extract, 2.0% pet	CD
4		<i>Evernia prunastri</i> (oakmoss) extract, 1.0% pet	SP
5		Fragrance mix I, 8.0% pet	CD and SP
6		Glutaraldehyde, 0.5% pet	CD
7		Glutaraldehyde, 0.2% pet	CD
8		<i>Myroxylon pereirae</i> resin, 25.0% pet	CD
9	2%	Decyl glucoside, 5.0% pet	CD
10	1%	Alpha-amylcinnamic aldehyde, 1.0% pet	SP
11		Cinnamic aldehyde, 1.0% pet	SP
12		DMDM hydantoin, 1.0% pet	CD
13		Formaldehyde, 1.0% pet	CD
14		Hydroxycitronellal, 1.0% pet	SP
15		2-Hydroxyethyl methacrylate, 2.0% pet	CD
16		Isoeugenol, 1.0% pet	SP
17		Melamine formaldehyde, 7.0% pet	CD
18		Methylisothiazolinone + methylchloroisothiazolinone, 0.01% pet	CD

TABLE 1 Updated commercially available patch test preparations containing different concentrations of sorbitan sesquioleate^a

Note: SSO, sorbitan sesquioleate; CD, Chemotechnique MB Diagnostics AB, Vellinge, Sweden; SP, SmartPractice Canada, Calgary, Canada & SmartPractice Europe GmbH, Barsbüttel, Germany.

^aInformation from info@smartpracticecanada.com and www.chemotechnique.se, September 2022.

TABLE 2 Demographic data, the intensity of reactions to sorbitan sesquioleate (SSO) 20% in petrolatum, and concomitant positive patch test reactions to the mixture of fragrance allergens in patients with SSO contact allergy

Case no.	Gender	Age (year)	AD	Patch test intensity to SSO (first/second reading) ^a	Clinical relevance of SSO allergy	Concomitant positive patch test reaction(s) ^b		
						Fragrance mix I (n = 221)	<i>Myroxylon pereirae</i> resin (n = 250)	<i>Evernia prunastri</i> extract (n = 77)
% Simultaneous positive reaction to sorbitan sesquioleate:						3.2%	4.0%	10.4%
1	Female	28	Yes	+/+	Unknown	—	—	—
2	Female	25	Yes	+/—	Unknown	—	—	—
3	Female	28	Yes	+/—	Unknown	—	—	—
4	Female	45	No	+/+	Unknown	—	—	—
5	Male	15	Yes	+/?	Yes	—	—	—
6	Female	49	No	+/?	Unknown	—	—	—
7	Female	52	Yes	+/?	Unknown	—	—	—
8	Female	61	No	+/?	Yes	—	+	—
9	Female	39	No	+/?	Unknown	—	+	—
10	Female	45	No	?/++	Yes	?	++	++
11	Male	55	No	+/++	Unknown	++	++	++
12	Male	63	No	+++ / ++	Yes	++	++	++
13	Female	32	No	++ / ++	Yes	++	+	++
14	Female	39	Yes	+/?	Unknown	+	+	+
15	Male	33	Yes	+/?	Unknown	+	+	+
16	Female	72	No	++ / +	Yes	++	++	+
17	Male	56	No	+/++	Yes	++	++	++

Note: AD, atopic dermatitis; —, negative; ?, doubtful reaction; +, weak positive reaction; ++, strong positive reaction; +++, extreme positive reaction.

^aThe first reading was performed on Day 3 or 4, whereas the second reading was performed on Day 7.

^bThe strongest reactions on either the first or second reading day are demonstrated.

extract but also to decyl glucoside 5% pet. (2+) and HEMA 2% pet. (1+). This patient did not react to other allergens, including FM II (14% pet.) and lauryl glucoside (5% pet.). Based on the prevalences at our clinic during the study period, the estimated likelihood that one patient would test positively to all these five preparations would be 2×10^{-8} .

DISCUSSION

The SSO contact allergy prevalence from this study (0.48%) remained similar to previous studies.^{10,18,19} The prevalence of contact allergy to SSO in Europe was from 0.2% to 1.5% and seemed to be higher in other continents.⁵ Our study found irritant reactions in only two patients suggesting that SSO could rarely cause skin irritation by patch testing. The result is in conjunction with several animal studies confirming that SSO is a mild irritant,¹ supports the fact that clearly irritative reactions are very unusual with the present patch test dose. However, to the best of our understanding, the present patch test dose for SSO has not been robustly defined in a structured manner.²⁰ Observing many patients with a doubtful reaction in this study might represent either a weakly allergic reaction that did not fulfil the criteria of a positive reaction or mild irritation without showing typical morphologies of an irritant reaction.¹⁶

The pattern of patch test reactivity for AD patients differed as doubtful and positive reactions were overrepresented. This indicates a possible association between AD and patch test reactions to SSO 20% in pet. There may be several explanations for this finding. (1) Degree of exposure: AD patients might be sensitized to SSO in topical corticosteroid medication or moisturising creams, which they are recommended to use to avoid dry skin.²¹ (2) Individuals with AD have a known impaired skin barrier due to a filaggrin (*FLG*) gene mutation and therefore may be prone to sensitisation to SSO, which is considered a weak allergen.²² (3) As the patch test dose has not been systematically investigated, another reason might be that the present test concentration is too high and irritate AD patients' skin. Hereby, the present SSO dose can be based on its skin irritation capacity in AD patients, give rise to doubtful reactions and false positive reactions defined as irritant patch test reactions with a morphology indistinguishable from an allergic patch test reaction. It might be of interest to further study the substance with regard to possible irritative properties of SSO in AD patients and, even more, the effect on the penetration of other allergens when the test preparations contain SSO.

Several patients had a weak positive reaction to SSO without simultaneous positive reactions to FM I, BOP and oakmoss extract. This could be explained by the SSO concentration in the mixture of allergens being lower than in the test preparation with SSO. In comparison, patients with a stronger reaction to SSO-alone were more likely to have simultaneous reactions to either FM I, BOP or oakmoss extract. Due to their strong reactivity to SSO, they would likely react positively to SSO at the lower concentration contained in several mixes. Mixing SSO into the preparations might also affect the patch

test results because SSO can increase the skin permeability of the test substances and may enhance the intensity of reactions.⁶

The interpretations of patch test reactions were challenging in several conditions when SSO-containing preparations were tested. When patients reacted positively to both SSO and FM I and/or BOP and/or oakmoss extract, fragrance contact allergy could not be ruled out unless all individual chemicals of the mixes had been tested. It is important to interpret the reactions carefully, particularly when SSO is added at a 5% concentration (Table 1). Although it was strongly indicated that a patient (no. 17) could have a contact allergy to SSO because the likelihood of reacting positively to these allergens would be 2 in 100 million, fragrance contact allergy might, however, be concealed.

In conclusion, this study cannot recommend SSO for screening in the baseline series due to the relatively low prevalence and difficulty in evaluating clinical relevance.²³ In case the purpose of including SSO for patch testing is to distinguish the diagnosis of contact allergy to the actual allergens labelled on the commercially available patch test syringes from SSO as an emulsifier, the interpretation remains highly problematic. Further research is needed to investigate the effects of SSO in patch test preparations and products available on the market. Using another emulsifier with virtually neither skin irritancy nor sensitising capacity should be a beneficial solution.

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CONFLICTS OF INTEREST

Magnus Bruze is a member of the Expert Panel for Fragrance Safety—<http://fragrancesafetypanel.org/>. Cecilia Svedman participates in the IDEA project sponsored by the International Fragrance Association (IFRA). The other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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