

Sorbitan Sesquioleate, a Common Emulsifier in Topical Corticosteroids, Is an Important Contact Allergen

Adam Asarch and Pamela L. Scheinman

Background: In the past, sorbitan sesquioleate (SSO) was reported as an uncommon allergen, but recent data suggest SSO may be an important sensitizer.

Objective: To present data on 13 of 112 dermatitis patients who reacted to SSO and/or sorbitan monooleate (SMO) on patch testing.

Methods: A retrospective data analysis was conducted on data from 112 dermatitis patients patch-tested from December 2006 to May 2007. All patients were tested with a modified North American Contact Dermatitis Group standard series, a cosmetic series, and a fragrance series.

Results: Of 112 patients, 10 (8.9%) reacted to SSO, 1 (0.9%) to SMO, and 2 (1.8%) to both. Nine of 12 (75%) SSO-positive patients were using topical corticosteroids emulsified with sorbitan derivatives or sorbitol; 2 of the 13 sorbitan-allergic patients were allergic to one or more corticosteroid screening chemicals tested.

Conclusion: SSO is a common emulsifier derived from sorbitol and is used in many high- to super-potent corticosteroids. It has only recently been identified as an important contact allergen. The high prevalence of reactions to sorbitol derivatives in this small group of patients suggests that these chemicals may be sensitizing when applied to dermatitic skin. Larger studies should be conducted to confirm these findings.

SORBITAN SESQUIOLEATE (SSO), derived from monoesters and diesters of oleic acid and hexitol anhydrides of sorbitol, is a common non-ionic emulsifier used in numerous medications and cosmetic products. Sorbitan monooleate (SMO) is also a non-ionic emulsifier but is derived from monoesters of oleic acid and hexitol anhydrides from sorbitol. SSO, in particular, functions as an emulsifier in a number of creams and lotions as well as in many topical corticosteroid preparations. In addition, SSO 5% is currently used as an emulsifier in fragrance mix I (FM I) for patch testing.¹⁻³ In the past, SSO has been reported as an uncommon allergen. In two large studies of patch testing with emulsifiers conducted approximately 20 and 30 years ago, the prevalence of allergy to SSO (tested at 20% in petrolatum) among dermatitis patients ranged from 0.5 to 0.9%.^{4,5}

Case reports have described contact allergy to both SSO and SMO. Contact dermatitis from SSO has been

reported to be caused by wound dressings and a topical corticosteroid preparation (patch-test concentrations of 20% and 10% in petrolatum, respectively).^{6,7} A recent case series of children also noted contact allergy to SSO (20% in petrolatum) in certain pediatric products as well as in topical corticosteroid preparations.⁸ Case reports have further reported that patients with leg ulcers had positive patch-test reactions to SSO 2% in petrolatum (pet), SMO 2% pet,⁹ and SMO 20% pet.¹⁰ A larger series of 23 leg ulcer patients found that 17% were allergic to SMO (10% pet) and that 13% were allergic to SSO (20% pet).¹¹

We report on 13 of 112 dermatitis patients who reacted to SSO 20% pet and/or SMO 5% pet from December 2006 to May 2007. In our study, 75% of sorbitan-positive patients were using a topical corticosteroid emulsified with SSO or sorbitol derivatives. We believe that the exposure to SSO in many topical corticosteroid preparations is responsible for the high prevalence of SSO reactions in our small series.

Materials and Methods

Among 119 consecutive patients referred for patch testing for all varieties of dermatitis from December 2006 to May 2007 at Tufts Medical Center, 112 consented for data

From the Tufts University School of Medicine, Boston, MA, and the Department of Dermatology, Tufts Medical Center, Boston, MA.

Address reprint requests to Adam Asarch, Tufts Medical Center, Department of Dermatology, 750 Washington Street, Box 116, Boston, MA 02111. E-mail adam.asarch@tufts.edu

DOI 10.2310/6620.2008.08013

© 2008 American Contact Dermatitis Society. All Rights Reserved.

analysis in an Institutional Review Board-approved study. Patients were tested with a modified North American Contact Dermatitis Group (NACDG) standard series, a cosmetic series, and a fragrance series. Other series were applied on the basis of history and physical examination.

All allergens were purchased from Chemotechnique Diagnostics (Vellinge, Sweden), except the individual FM I components, which were purchased from Hermal (Reinbek, Germany). FM I is emulsified with SSO 5% pet whereas the individual FM I components are all emulsified with SSO 1% pet. Ethyleneurea/melamine formaldehyde (EU/MF), present in our standard series, is also emulsified with SSO 5%. Our cosmetic series includes SSO 20% pet and SMO 5% pet. Allergens were placed in Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) and were occluded for 48 hours. Readings were performed at 48 and 72 hours, and reactions were graded according to the NACDG grading system: + (weak reaction: papules with erythema), ++ (strong reaction: papules plus edema or vesiculation), or +++ (extreme reaction: spreading papulovesicles and/or bullae). The results presented herein are those seen at the 72-hour reading.

We performed retrospective chart reviews on the 13 patients who reacted to SSO, SMO, or both. We evaluated for sex, race, age, history of atopy, and dermatitis localization among the sorbitan-positive patients. We also examined concurrent allergens among this group. We then reviewed product use, focusing on products containing SSO or SMO. We attempted to obtain follow-up data on all 13 sorbitan-reactive patients through contact with either the patients or their referring physicians.

Results

Demographics

The ages of the 13 patients who reacted to SSO, SMO, or both ranged from 12 to 69 years (mean, 47 years). The duration of the dermatitis ranged from 5 months to 10 years (mean, 2.3 years). Eleven patients (84.6%) were Caucasian, 1 patient (7.7%) was African American, and 1 patient (7.7%) was Asian. Eight patients (61.5%) were female, and 5 patients (38.5%) were male. Seven patients (53.8%) had a positive atopic history including seasonal allergies, asthma, or eczema. The dermatitis on presentation was localized to the upper extremity (arms and hands) in 69.2% of patients, lower extremity (legs and feet) in

61.5%, face in 38.5%, genital area or groin in 38.5%, lips in 7.7%, and neck in 7.7%.

SSO, SMO, and Other Allergens

In our analysis of SMO and SSO reactivity, 10 of 112 patients (8.9%) exhibited SSO allergy only, 1 of 112 patients (0.9%) demonstrated SMO allergy only, and 2 of 112 patients (1.8%) had a combined SSO and SMO allergy. Thus, 13 of 112 patients (11.6%) had either an SSO or SMO allergy.

We further classified allergen reactivity among the SSO- and SMO-allergic patients. The top five allergens in the standard series among these 13 patients were FM I (62%), potassium dichromate (62%), balsam of Peru (54%), nickel (31%), and bacitracin (31%) (Table 1).

Fragrance and EU/MF Allergy

As mentioned previously, FM I, a screening chemical for fragrance allergy, is generally emulsified with 5% SSO pet. Previous trials showed an improved yield of reactions to FM I constituents when FM I was emulsified with SSO.^{1,2} Eight of our 13 patients reacted to FM I; 6 of these 8 FM I responders also demonstrated allergy to balsam of Peru, another screening chemical for fragrance allergy that does not contain SSO. Of the 8 FM-I-positive patients, 6 patients also reacted to at least one of the eight individual components of the mix emulsified with 1% SSO; 4 of these 6 patients also reacted to balsam of Peru. We then further evaluated reactivity to individual fragrance chemicals that were not emulsified with SSO. None of the eight FM-I-positive patients showed definitive positive reactions to other fragrance chemicals that were not part of FM I. However, two patients did show "1+ weak" reactions to rose oil absolute 2% pet and lavender absolute 2% pet. These same two patients also had positive reactions to balsam of Peru and should therefore be considered

Table 1. Top Five Allergens in Standard Series

Rank	Allergen	Frequency of Patients Reacting
1	Fragrance mix I	8/13 (62%)
1	Potassium dichromate	8/13 (62%)
2	Balsam of Peru	7/13 (54%)
3	Nickel	4/13 (31%)
3	Bacitracin	4/13 (31%)

fragrance allergic. One of the 13 patients was negative to FM I, individual FM I components, and balsam of Peru, but had a "1+ weak" reaction to narcissus absolute. Another of the 13 patients was negative to FM I and balsam of Peru but had a + reaction to 1% cinnamyl alcohol in 1% SSO. One of the 8 FM I-positive patients also reacted to the cinnamic aldehyde 1% pet in our standard series (not emulsified with SSO).

EU/MF is also emulsified with SSO 5%. Two of the 13 sorbitan-positive patients were also allergic to EU/MF. However, both patients also reacted to formaldehyde 1% aqueous (aq), which does not contain SSO. This also suggested a true formaldehyde allergy among these patients and not simply a reaction to SSO.

Intensity of Reactions

Twelve of the 13 sorbitan reactors had + reactions to SSO, and one patient had a +++ reaction to SSO. The three patients who reacted to SMO had ++ reactions to SMD.

Co-Allergens in the Standard Series

Five of the 13 sorbitan reactors had at least five positive reactions to chemicals in our standard series (a total of 45 allergens are in our standard series). One patient had more than 10 reactions to allergens in the standard series. This patient showed a ++ reaction to SMO and a + reaction to SSO. Only 1 of the 13 patients reacted to paraben mix; 3 patients reacted to lanolin alcohol, and 1 patient reacted to sorbic acid in the cosmetic series. None of our patients had leg ulcers.

Tests with Other Series

All of our patients were tested with our standard, cosmetic, and fragrance series. Of the 13 patients with sorbitan allergy, 8 were tested with a textile series (Chemotechnique Diagnostics) because of a suspected textile allergy. All 8 of these patients reacted to at least one textile allergen. The three most common textile allergens for these patients were Disperse Blue 106 (38%), Reactive Blue 238 (31%), and Disperse Blue 124 (23%).

One patient was tested with a hair series, 2 patients with a rubber series, and 1 patient with a bakery series (all allergens in these series were provided by Chemotechnique Diagnostics). Of these patients, 1 reacted to ammonium persulfate in the hair series; 1 reacted to N-cyclohexyl-N'-phenyl-4-phenylenediamine, N,N'-diphenyl-4-phenylene-

diamine, and dibutylthiourea in the rubber series; and 1 reacted to benzoic acid in the bakery series.

Corticosteroid Allergy

We screen for corticosteroid allergy with the following chemicals in our standard series: tixocortol-21-pivalate (group A), budesonide (group B), dexamethasone-21 phosphate disodium (group C), and hydrocortisone-17-butyrate (group D2). We compared SSO responders to SSO nonresponders in the group of 112 patients. Two of 13 (15.4%) sorbitan-positive patients exhibited a concurrent corticosteroid allergy. One of these patients reacted to all four corticosteroid screening chemicals (groups A, B, C, and D2), and one patient reacted only to tixocortol-21-pivalate (group A). We then compared these results to those of the remaining 99 sorbitan-negative patients. Of interest, only 2 of 99 (2.0%) sorbitan-negative patients demonstrated a corticosteroid allergy. One of these patients reacted to tixocortol-21-pivalate, and one reacted to budesonide. Taken together, 2 of 4 (50%) patients with a corticosteroid allergy had a concurrent sorbitan allergy ($p = .07$). Although these results did not reach statistical significance, we feel they are important, given our small sample size.

Product Use

Strikingly, 9 of 12 (75%) SSO-positive patients were using topical corticosteroids emulsified with sorbitol or sorbitan derivatives. Two of 13 (15%) SSO- and SMO-positive patients were using topical antifungals emulsified with sorbitan derivatives. Finally, 13 of 13 (100%) SSO- and SMO-positive patients were using products containing sorbitan derivatives or sorbitol, which suggests that they had become sensitized to these chemicals in their products.

Patient Follow-Up

We were able to follow up 9 of the 13 total patients (69.2%) for 6 months to 1 year after patch testing. Eight of 9 of these patients (88.9%) showed improvement with our recommendations, which included avoidance of proven contact allergens. Seven of 9 SSO-positive patients, who had originally been using topical steroids emulsified with SSO and/or sorbitol, showed improvement with an initial switch to a non-SSO-containing or nonsorbitol-containing steroid in addition to our other recommendations.

Table 2. Partial Listing of Steroids Containing Sorbitan Sesquiolate

<i>Steroid Group</i>	<i>Steroid</i>	<i>Potency</i>
D1	Clobetasol propionate ointment	Super
	Halobetasol propionate ointment	Super
	Betamethasone dipropionate ointment	Super
	Fluticasone propionate ointment	High
C	Desoximetasone ointment	High
B	Fluocinonide ointment	High
A	Hydrocortisone acetate ointment	Low

Discussion

SSO is a common emulsifier used in many corticosteroid ointments, medicaments, and some cosmetics. Table 2 provides a partial listing of super-, high-, and low-potency steroids that contain SSO. Steroids from groups A, B, C, and D1 can contain SSO. Although we did not find any group D2 corticosteroids to contain SSO directly, we did discover sorbitol in a number of group D2 steroid formulations. Numerous steroids of all potencies and from all classes can contain sorbitol. Coloe and Zirwas recently reported that 47 of 166 topical corticosteroids contain SSO or a cross-reactor.¹² The sheer volume of different corticosteroids containing SSO provides patients with ample opportunity for exposure to this emulsifier on dermatitic skin and subsequent sensitization.

Previous studies evaluating SSO as an allergen found it to be relatively insignificant. Frosch and colleagues, in a study on FM I and its constituents with and without SSO, found that only 0.7% of their patients (5 of 709) reacted to SSO.¹ Enders and colleagues found no SSO allergy in 721 patients tested with FM I and constituents with SSO.² Hannuksela and colleagues, in studies on a wide range of emulsifiers, found that only 6 of 1,206 patients (0.5%) were allergic to SSO.⁴ Tosti and colleagues, in studies on emulsifiers in patients with suspected dermatitis from cosmetics and medicaments, found that only 7 of 737 patients (0.9%) were allergic to SSO.⁵ These studies, which were performed more than 10 and 30 years ago, suggested that SSO was not an important allergen at those times. We hypothesize that many more corticosteroids have been emulsified with SSO since then. The use of superpotent topical steroids such as clobetasol or halobetasol ointment (often as first-line therapy for many dermatitis patients) has perhaps also contributed to sensitization to SSO.

The clinical characteristics for our patients were similar to those found in national studies. Mean age, female predominance, and race distribution were all similar.^{13,14}

Four of the top five allergens for our SSO-positive patients (FM I, balsam of Peru, nickel, and bacitracin) were among the top 10 allergens reported by the NACDG for the 2003–2004 study period.¹⁴

We found a high prevalence of fragrance allergy in our sorbitan-positive patients, which was similar to prevalence data from the NACDG.¹⁴ Our results suggest that at least 6 of 8 patients with FM I reactions had a true fragrance allergy and were not just reacting to the SSO in FM I. Those who reacted to balsam of Peru and the patient who reacted to cinnamic aldehyde from Chemotechnique (containing no SSO) were not simply reacting to SSO. Nonetheless, as Orton and Shaw reported, it is important to test for SSO when evaluating for FM I reactivity, to avoid false-positive results.¹⁵

In our study, SSO was substantially more prevalent as an allergen than was SMO. Cross-sensitization to these two emulsifiers was observed in only 1.8% of patients. Given the similar chemical structures of the two compounds, these results were somewhat surprising. Fewer patients may have reacted to SMO than to SSO, given its lower concentration (only 5% pet for SMO vs 20% pet for SSO) in the patch-test formulations. The difference in concentration could account for the variation in reactivity. Pasche-Koo and colleagues found greater reactivity to SMO (17% of patients) than to SSO (13% of patients) among leg ulcer patients, but in their series, SMO was tested at a concentration of 10% pet.¹¹ Improved yields for SMO in patch testing may be noted at higher concentrations. Examining elicitation thresholds for both allergens at 20%, 10%, 5%, and 1% may be helpful in determining optimal concentrations for SSO and SMO in patch testing.

Conclusion

Whereas the potential for topical steroids to induce contact dermatitis is well studied,^{16–19} researchers are now recognizing an independent association between sorbitan emulsifiers, corticosteroid use, and the development of allergic contact dermatitis.^{7,8,12} Our data further confirm this trend. The high prevalence of contact reactions to SSO in our small group of patients suggests that SSO is an important allergen, particularly when applied to dermatitic skin. It is likely that the common use of topical corticosteroids emulsified with SSO in dermatitis patients has contributed to contact sensitization to SSO among these patients. Through our recent analysis, we hope to alert the dermatologic community to this largely unrecognized relationship. We believe that larger studies of

dermatitis patients should be conducted to confirm these interesting findings.

References

1. Frosch PJ, Pilz B, Burrows D, et al. Testing with fragrance mix. Is the addition of sorbitan sesquioleate to the constituents useful? *Contact Dermatitis* 1995;32:266–72.
2. Enders F, Przybilla B, Ring J. Patch testing with fragrance-mix and its constituents: discrepancies are largely due to the presence or absence of sorbitan sesquioleate. *Contact Dermatitis* 1991;24:238–9.
3. Pereira F, Cunha H, Dias M. Contact dermatitis due to emulsifiers. *Contact Dermatitis* 1997;36:114.
4. Hannuksela M, Kousa M, Pirila V. Contact sensitivity to emulsifiers. *Contact Dermatitis* 1976;2:201–4.
5. Tosti A, Guerra L, Morelli R, Bardazzi F. Prevalence and sources of sensitization to emulsifiers: a clinical study. *Contact Dermatitis* 1990;23:68–72.
6. de Waard-van der Spek FB, Devillers AC, Oranje AP. Allergic contact dermatitis to sorbitan sesquioleate in Adaptic wound dressing. *Contact Dermatitis* 2007;57:54–6.
7. Green C, Kenicer KJ. A case of “contact allergy to corticosteroid.” *Contact Dermatitis* 1993;28:39–40.
8. Castaneda-Tardan MP, Jacob SE. Allergic contact dermatitis to sorbitan sesquioleate in children. *Contact Dermatitis* 2008;58:171–2.
9. Mallon E, Powell SM. Sorbitan sesquioleate—a potential allergen in leg ulcer patients. *Contact Dermatitis* 1994;30:180–1.
10. Wakelin SH, Cooper S, Marren P, Shaw S. Sorbitan mono-oleate: a potential allergen in paste bandages. *Contact Dermatitis* 1996;35:377.
11. Pasche-Koo F, Piletta PA, Hunziker N, Hauser C. High sensitization rate to emulsifiers in patients with chronic leg ulcers. *Contact Dermatitis* 1994;31:226–8.
12. Coloe J, Zirwas MJ. Allergens in corticosteroid vehicles. *Dermatitis* 2008;19:38–42.
13. Davis MD, Scaf LA, Yiannias JA, et al. Changing trends and allergens in the patch test standard series: a Mayo Clinic 5-year retrospective review, January 1, 2001, through December 31, 2005. *Arch Dermatol* 2008;144:67–72.
14. Warshaw EM, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2003–2004 study period. *Dermatitis* 2008;19(3):129–36.
15. Orton DI, Shaw S. Sorbitan sesquioleate as an allergen. *Contact Dermatitis* 2001;44:190–1.
16. Burden AD, Beck MH. Contact hypersensitivity to topical corticosteroids. *Br J Dermatol* 1992;127:497–500.
17. Isaksson M, Andersen KE, Brandao FM, et al. Patch testing with corticosteroid mixes in Europe. A multicentre study of the EECDRG. *Contact Dermatitis* 2000;42:27–35.
18. Davis MD, el-Azhary RA, Farmer SA. Results of patch testing to a corticosteroid series: a retrospective review of 1188 patients during 6 years at Mayo Clinic. *J Am Acad Dermatol* 2007;56:921–7.
19. Doooms-Goossens A, Morren M. Results of routine patch testing with corticosteroid series in 2073 patients. *Contact Dermatitis* 1992;26:182–91.