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Allergic contact dermatitis from potassium sorbate and sorbic acid in topical pharmaceuticals and medical devices

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ABSTRACT

Background. The preservatives sorbic acid (SA) and potassium sorbate (PS) are considered rare skin sensitizers. PS-containing products always contain SA to a certain extent, and positivity to PS may reflect sensitization to SA. Their optimal patch test conditions are unknown.

Objectives. To report on the outcome of testing with SA and PS in various concentrations and/or vehicles.

Patients and methods. Seventeen patients with allergic contact dermatitis from PS/SA-containing topical pharmaceuticals and medical devices were patch tested to SA 2% and 5% pet., SA 1%, 2%, 3%, 5%. eth., and/or SA 2% aq., whereas PS was patch tested at 5% pet. and/or 5% aq.

Results. Only one patient, not tested to the ethanol preparations, presented with a (doubtful) positive reaction to SA 2% pet., while this remained negative in 13 patients who reacted to SA 2% eth. The preparations containing SA 5% pet., 1%, 3%, and 5% eth., and SA 2% aq. had little or no additional value. PS 5% pet. performed better than 5% aq., and always mirrored SA sensitization.

Conclusions. Sensitization to SA and PS is probably underestimated. SA 2% eth. and PS 5% pet. are preferred for patch testing, and patients sensitized to SA should avoid PS-containing products.

INTRODUCTION

Sorbic acid (SA) and its salt potassium sorbate (PS) (**Figure 1**) are preservatives used in food, cosmetics and topical pharmaceutical products, the latter including commercialized topical antibiotics (AB), or combinations of corticosteroids with antibiotics (CS/AB), and compounded pharmaceutical corticosteroid creams (CPC). Moreover, PS and SA may also be incorporated in medical devices, such as wound care products (WCP), anti-scar creams, ultrasound gels, and sexual lubricants **(1)**.

Although PS has a lower antimicrobial potency than SA, it is more frequently used, because it is less volatile and has a greater solubility in water, i.e., in that phase of products in which microorganisms reside **(2).** Moreover, in an aqueous environment, PS will always partially dissociate into SA, depending on the pH. Consequently, PS-containing products always contain some SA, and patients sensitized to the latter should avoid their use **(3)**. In Europe, SA and PS are used in topical products up to 0.6% and 0.8%, respectively, whereas in the U.S. both preservatives may be present up to 1%. Most topical products contain rather low concentrations though, usually between 0.05% (500 ppm) and 0.3% (3000 ppm) **(1, 2)**, however, still capable of inducing skin sensitization **(4)**. Although considered rare, PS/SA may induce contact allergy and subsequent allergic contact dermatitis (ACD), especially when used on damaged (inflamed) skin **(1)**.

SA has been patch tested at 2% in petrolatum [pet.], 2% in ethanol [eth.], 2.5% eth., 3% pet., and 5% pet., of which only the former two are currently commercialized as patch test preparations **(1, 5)**. PS may be patch tested at 5% pet., or occasionally 5% aq., but neither one of these is commercially available **(1)**.

Here we report our experience with patch testing SA and PS in various concentrations and/or vehicles, mainly focusing on the different outcome of patch tests with SA 2% pet. and 2% eth., and PS 5% pet. and 5% aq., as well as on the relationship between PS and SA sensitization.

PATIENTS AND METHODS

The medical files of 17 patients, attending the University Hospital Antwerp (UZA) and the Imelda Hospital Bonheiden (IHB) during the period between January 2018 and March 2020, who had suffered from suspected ACD due to PS/SA-containing topical pharmaceutical products or medical devices, were retrospectively reviewed. All patients had been patch tested with a baseline series, additional series, and with the suspected SA/PS-containing products 'as is'. At UZA, SA and PS were always patch tested at 2% pet. (Chemotechnique Diagnostics, Vellinge, Sweden) and 5% pet. (in-house preparation), respectively. From January 2019 onwards, SA was occasionally also patch tested at 5% pet., 1%, 2%, and/or 5% eth., while PS was occasionally also patch tested at 5% aq. (all in-house preparations). SA 2% pet. and occasionally also 2% aq., 3% and 5% eth., but not PS, were tested in IHB.

When a CPC was involved, containing the cream base "cremor cetomacrogolis"(CMC) plus a corticosteroid, this cream base and its main vehicle component (cetearyl alcohol 20% pet.), as well as the corticosteroids used, were usually patch-tested separately. In case commercialized CS/AB and AB products had been used, their active ingredients (corticosteroids and/or fusidic acid) and (some of) their vehicle components (e.g. parabens) were also patch-tested. Ingredients of the WCP and of sexual lubricants, other than SA/PS, were not available for patch testing. Some patients had undergone multiple patch test sessions to exclude co-sensitization to other (active or vehicle) ingredients.

The Allergeaze (SmartPractice, Calgary, Canada) and IQ Ultra™ patch test chambers (Chemotechnique Diagnostics) were used at UZA and IHB, respectively. All patch tests were always occluded for two days on the upper back with Fixomull Stretch (BSN medical, Hamburg, Germany), and were read according to ESCD guidelines on day D2 and D4, and sometimes also later (e.g. D7 in case of patch tests to corticosteroids) **(6)**. Alternatively, when late readings were not possible at the clinic, patients were instructed to send photographs by e-mail (**7**).

RESULTS

The results of all patch test investigations are summarized in **Table 1**. The 17 patients concerned 10 females and 7 males with an age range from 33 to 93 years old (median and mean ages of 67 and 63 years old, respectively). Most patients (15/17) had a pre-existent dermatosis (1 psoriasis and 14 eczema) for which they had applied several topical products; two patients had developed genital ACD following the use of a sexual lubricant.

Twenty-five PS/SA-containing topical products suspected to have caused or aggravated the dermatitis of the patients included 3 CS/AB, 4 AB, 11 CPC, 5 WCP, and 2 sexual lubricants; these all contained, according to their labels, PS, and/or to a lesser extent SA.

Twenty-three of 25 culprit products had been patch tested 'as is' (with some patients using more than 1 product) and twenty-two of these (96%) had resulted in positive patch test reactions: 16 ++, 4 +, and 2 ?+.

With regard to the patch test results of SA and PS, the following can be summarized: SA 2% pet. patch tested negatively in all but one patient, whereas 1/17 and 12/17 patients had a ++ and + reaction to SA 2% eth., respectively. The latter, however, also included two patients (no. 2 and 8) in whom irritancy could not be excluded, neither to the 2%, nor to the SA 5% eth. In two other patients (no. 12 and 13) SA 3% and 5% eth. had been patch tested, instead of SA 2% eth., both resulting in strong (++) positive reactions. Patch testing SA in aq., in lower concentrations in eth. (1%), or in higher concentrations in pet. (5%) had little additional value. PS 5% pet., rather than 5% aq., resulted in positive reactions (ranging from ?+ to ++), that is, in 5/15 patients, all of whom also had positive patch test reactions to one or more SA-containing test preparations.

In all patients the positive patch tests to SA/PS were felt to be relevant, as the culprit SA/PS-containing products had also resulted in clearly positive patch tests in the majority of cases.

Patients were often co-sensitized to other contact allergens (data on file), some of these equally contributing to their dermatitis. The latter also included co-reactions to active ingredients (e.g. corticosteroids and antibiotics in patient no. 4) and vehicle components (e.g. cetearyl alcohol 20% pet. in patient no. 9) present in the culprit products. As not all patients could be patch tested to all components of the culprit products, some co-sensitizations might have been missed though.

Interestingly, 12/17 patients who had experienced aggravation of their dermatitis by a CPC had always co-reacted to the cream base CMC "as is" (without the corticosteroid) suggesting contact allergy to a vehicle component (**Figure 2**). As cetearyl alcohol 20% pet., another vehicle component of this cream, was negative in all but one of these patients, the ingredient PS/SA was a likely suspect, mostly confirmed by patch testing SA 2% eth.

DISCUSSION

Most data on contact sensitization from SA and PS have been derived from case reports, often describing iatrogenic sensitization to SA from the presence of PS and/or SA in topical pharmaceutical products (**1, 3-5, 8-12**). Although considered to be a rare sensitizer, some reports detail that SA sensitization might occur in ~1% of patch-tested individuals (**9, 13-14**), suggesting that contact allergy to this preservative might be more frequently occurring than generally assumed, particularly in certain populations (e.g. patients with pre-existent dermatitis and/or leg ulcers)(**1**).

In order to reliably estimate the sensitization rate of a substance, it is imperative to use the most appropriate patch test concentration and vehicle, which is, however, not known for SA and PS. According to former reports, it was SA 5% pet. that was used (**3, 9-11**), but this concentration was apparently lowered to SA 2% pet. (**4, 8, 12**), whereas SA 2.5% eth. was only exceptionally patch tested (**5**). For example, in the seventies, Göransson K. et al. observed 21 cases of ACD from the SA-containing Unguentum Merck, for which the authors could identify SA as the responsible contact allergen in 19 of them (90%) by using the 2.5% eth. patch test preparation (**5**).

SA is almost insoluble in water, in which it readily precipitates (**2**), thus rendering patch testing with SA in aq. virtually impossible (e.g. Patients 12 and 13, both negative to SA 2% aq.). Conversely, SA can easily be diluted in eth. and pet., but patients react to SA 2% eth. rather than to SA 2% pet. Patch test preparations should be formulated in such a way that the component under investigation (i.e. SA) has a maximum tendency to leave the vehicle and penetrate into the skin. The pet. preparation might lead to false-negative results because SA has a higher affinity towards an oily phase (such as pet.), as compared to eth., thus obstructing the release of SA from a pet. patch test preparation (**2,15**). Additionally, when dispersed in eth., SA likely also has a greater affinity for the oily phase of the skin, hence favouring its penetration

from the eth. vehicle into the skin. Furthermore, eth. is known to be a 'skin penetration enhancer' (SPE) (**16-18**).

The latter may explain why the PS/SA-containing pharmaceutical products and medical devices, responsible for the observed ACD, usually resulted in strong (++) positive patch test reactions. Indeed, commercialized products for topical use on the skin usually have an excellent oil/water-balance, and often contain several SPEs, such as emulsifiers, thus acting as more appropriate patch test vehicles for SA (**16-18**). Nevertheless, occasionally an SA-containing product may not show a positive patch test reaction in contrast to SA itself (e.g. Patient 16).

Cases 4, 12, and 13 may illustrate this: similar to the other patients reported herein, these 3 adults had suffered from ACD due to topical products (CS/AB, AB and CPC) prescribed to treat a pre-existent dermatitis. Surprisingly, they had shown strong (++) patch test reactions to the products used, but not to their common ingredient SA patch tested at 2% pet. When additionally patch tested to SA 2%, 3%, and/or 5% eth., (strong) positive results were, however, observed. Importantly, these cases further illustrate that, before a diagnosis of a so-called 'compound' contact allergy (i.e., to a newly formed allergen from other components present in the product) is put forward, one has to wonder if all ingredients, including the excipients, have been patch tested in an appropriate vehicle and/or concentration. This is in line with a recent paper in which it could be demonstrated that ACD from the CMC cream base cannot be the result of such a compound allergy, since chemical analyses failed to detect any additional compound(s) in it (**19**). Besides, in the cases those authors described, PS/SA were the likely culprits as well.

From the current data, it appears that SA 2% eth. is more suitable than SA 2% pet. to diagnose contact allergy to this preservative. Increasing the patch test concentration to 5% in pet. does not seem to be superior in this regard, whereas SA 5% in eth., although potentially yielding more positive reactions, also increases skin irritancy, hence complicating the interpretation of the patch tests. Given that SA 2% eth. usually results in 1+ patch test reactions, with some of them occasionally also difficult to differentiate from irritant reactions, lowering of the patch test concentration to 1% eth. might be considered, although this, in turn, might underestimate SA-sensitization.

Potassium sorbate (PS) is, contrary to SA, strongly water soluble, thus an aqueous patch test solution should be appropriate. However, the tendency of PS to leave this vehicle, and effectively penetrate into the skin, may be rather modest (**15-17**). PS can also be dispersed in

pet., for which its lower affinity, but in contrast higher affinity for the hydrophilic (aqueous) parts of the skin, will render its release from the pet. preparation and skin penetration more likely. Consequently, this might explain why the PS 5% pet. appears to be more effective than PS 5% aq. in revealing contact allergy to this particular substance, albeit that the numbers are low and that no direct comparison was made. Due to the absence of water, SA cannot be formed in PS 5% pet. patch test preparations, but it might be formed secondarily, either in the skin, or following occlusion (i.e., hidropoiesis). However, its likely low concentration might explain the predominantly negative patch test results.

Some authors suggest that a positive patch test to PS 5% pet. actually reflects sensitization to SA (**3**). As shown in the present series, PS (5% pet. and/or 5% aq.) remained often negative, and when a positive patch test did occur, it was always accompanied by a positive patch test to SA, confirming that sensitization to PS indeed most likely mirrors sensitization to SA. Nevertheless, concomitant sensitization to PS and SA may not be fully excluded in some cases, and, similar to SA, also higher patch test concentrations for PS might be worthwhile. Future research may inform us whether PS may be considered as an independent sensitizer in its own right.

LIMITATIONS OF THIS STUDY

Apart from its retrospective design, with potentially incomplete information on all products used, this study also dealt with only a small sample of patients, the majority having a compromised skin barrier (i.e. a pre-existent psoriasis or eczema), and who were often using multiple (SA/PS-containing) products. Such conditions might facilitate polysensitization, including contact allergy to weak sensitizers such as SA/PS. Whether our observations can be extrapolated to patients with non-damaged skin, and/or to SA/PS-containing cosmetics, remains to be demonstrated. In this regard, it is interesting to note that for the screening of contact allergy to SA in cosmetics currently the pet. preparation is recommended (**20**). Another limitation is that late readings (≥ D7) were not always performed "live" at the clinic, although SA 2% pet. may occasionally give rise to late and weak (+) reactions (**12**). Finally, although active ingredients (corticosteroids, antibiotics) and vehicle components of the culprit products were often patch-tested, this was sometimes not feasible, due to the unavailability of ingredients and/or patients not willing to be re-tested; relevant co-sensitizations might thus have been missed. Nevertheless, this should not distract from the fact that a relevant contact allergy to SA/PS may occur, and be overlooked, if SA 2% eth. is not patch tested, which this paper aimed to demonstrate.

CONCLUSION

Topical pharmaceutical products and medical devices, often applied to damaged skin, may induce contact sensitization to SA/PS, particularly SA. In order to optimize the detection of contact allergy to SA a patch test to 2% eth. instead of, or at least along with, 2% pet. should be considered. PS is preferably patch tested at 5% pet. and positivity to it likely reflects sensitization to SA, indicating that patients sensitized to SA should indeed also avoid the use of PS-containing products.

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Table 1: Characteristics and patch test results of 17 patients with suspected allergic contact dermatitis from 25 potassium sorbate (PS)/sorbic acid (SA)-containing topical pharmaceutical products and medical devices.

PATIENT	**Sex/ age**	**Dermatosis (localisation, duration)**	**Culprit product** (containing PS and/or SA)	**Culprit product (D4)**	**SA 2% pet (D4)**	**SA 5% pet (D4)**	**SA 1% eth (D4)**	**SA 2% eth (D4)**	**SA 5% eth (D4)**	**PS 5% pet (D4)**	**PS 5% aq (D4)**	**Positive patch tests to other (active or vehicle) ingredients of the culprit PS/SA-containing products**
1	F/93	Periulcer dermatitis (legs, 9 months)	**WCP** (PS)	NT	?+	NT	NT	NT	NT	++	NT	NT
2	M/72	Periulcer dermatitis (legs, 3 years)	**WCP**(PS)	?+	--	--	NT	+/IRR	+/IRR	?+	NT	NT
3	F/33	Generalized dermatitis (full body, 2 years)	**CPC** (PS)	+	--	NT	NT	+	NT	+	NT	CMC cream base: + cetearyl alcohol 20% pet. – corticosteroids: --

4	M/69	Ear dermatitis (ears, 2 years)	**CPC** (PS) **CS/AB** (PS)	++ NT	--	--	NT	+	+	--	NT	CMC cream base: ++ cetearyl alcohol 20% pet. -- corticosteroids: HCA ?+, HCB++, DXM ++, BMDP ++, BMV + fusidic acid ++ paraben mix: --
5	F/62	Periulcer dermatitis (legs, 1.5 years)	**CPC** (PS)	++	--	--	NT	--	++	--	NT	CMC cream base: ++ cetearyl alcohol 20% pet. -- corticosteroids: NT
6	M/70	Psoriasis (full body, 3 years)	**CPC** (PS)	++	--	--	NT	+	+	--	NT	CMC cream base: ++ cetearyl alcohol 20% pet. -- corticosteroids: --
7	F/67	Generalized dermatitis (full body, 6 months)	**CPC** (PS)	++	--	--	NT	++	+/IRR	--	NT	CMC cream base: ++ cetearyl alcohol 20% pet. – corticosteroids: --
8	F/69	Generalized dermatitis (full body, 5 months)	**CPC** (PS)	?+	--	--	NT	+/IRR	+/IRR	--	NT	CMC cream base: ?+ cetearyl alcohol 20% pet. – corticosteroids: NT

9	M/72	Periulcer dermatitis (full body, >20 years)	**CPC** (PS) **WCP** (PS)	+ NT	--	+	+	+	NT	+	?+	CMC cream base: + cetearyl alcohol 20% pet. + corticosteroids: -- other ingredients of the WCP: NT
10	M/67	Generalized dermatitis (full body, 2 years)	**CPC** (PS)	++	--	--	--	+	NT	--	--	CMC cream base: ++ cetearyl alcohol 20% pet. – corticosteroids: NT
11	F/72	Periulcer dermatitis (legs, 2 months)	**CPC** (PS) **AB** (PS) **WCP** (PS)	+ ++ ++	--	--	--	+	NT	--	--	CMC cream base + cetearyl alcohol 20% pet. – corticosteroids: NT fusidic acid – BHA: NT

												other ingredients of the WCP: NT
12	M/75	Truncal dermatitis (trunk, 4 months)	**CPC** (PS) **CS/AB** (PS) **AB** (PS)	++ ++ ++	--	NT	NT	NT (SA 3% eth. ++); SA 2% aq. --	++	NT	NT	CMC cream base ++ cetearyl alcohol 20% pet. – corticosteroids – fusidic acid: NT paraben mix: -- BHA: NT
13	F/58	Facial dermatitis (face, 6 months)	**CPC** (PS) **CS/AB** (PS) **AB** (PS)	++ ++ ++	--	NT	NT	NT (SA 3% eth. ++); SA 2% aq. --	++	NT	NT	CMC cream base ++ cetearyl alcohol 20% pet. – corticosteroids: -- fusidic acid NT paraben mix: -- BHA: NT
14	M/49	Periulcer dermatitis (legs, 7 years)	**WCP** (PS)	+	--	--	?+	+	NT	--	--	NT

15	F/44	Genital dermatitis (genitals, 5 years)	**Sexual lubricant** (PS)	++	--	--	--	+	NT	--	--	NT
16	F/55	Genital dermatitis (genitals, several years)	**Sexual lubricant** (SA,PS)	--	--	--	--	+	NT	--	--	NT
17	F/52	Facial dermatitis (face, 8 months)	**CPC** (PS)	++	--	--	+	+	NT	+	--	CMC cream base ++ cetearyl alcohol 20% pet. – corticosteroids NT

PS: potassium sorbate / SA: sorbic acid / F = female / M = male / D = day / pet. = petrolatum / eth. = ethanol / aq. = aqua / NT = not tested / +/IRR = a positive patch test reaction (+), but irritancy could not be excluded / -- negative patch test reaction.

HCA: hydrocortisone acetate /HCB: hydrocortisone butyrate/DXM: dexamethasone/BMDP: betamethasone dipropionate/BMV: betamethasone valerate/BHA: butyl hydroxyl anisole

WCP: **wound care product**, in all cases Flaminal® Forte gel (Flen Health, Kontich, Belgium) containing PS, alginate, macrogol, glucose oxidase, lactoperoxidase, glucose, guaiacol, potassium iodide, buffer, and purified water.

CPC: compounded pharmaceutical corticosteroid cream, in all cases formulated using the cream base "cremor cetomacrogolis (CMC)", to which all patients showed a positive patch test reaction, indicating contact allergy to a vehicle component.

CMC cream base: "cremor cetomacrogolis", containing PS (or occasionally SA) and cetostearyl alcohol as main vehice components; other ingredients include cetomacrogol 1000, white petrolatum, liquid paraffin, sodium dihydrogen phosphate dehydrate, diluted phosphoric acid or sodium hydroxide, and purified water.

CS/AB: commercialized combination corticosteroid/antibiotic cream, in all cases Fucicort® (Leo Pharma, Lier, Belgium) containing the combination of fusidic acid and betamethasone valerate (BMV) as active ingredients, whereas the vehicle components include PS, cetostearylalcohol, methyl-and propyl paraben, but also tocopherol, steareth-21, liquid paraffin, hypromellose, citric acid monohydrate, and purified water.

AB: commercialized antibiotic cream, in all cases Fucidin® (Leo laboratories Ltd., Dublin, Ireland) or Affusine® (Basic Pharma Manufacturing BV, Geleen, The Netherlands) both containing fusidic acid as active ingredient whereas the vehicle components include PS, buthylhydroxyanisol (BHA), cetylalcohol, polysorbate 60, glycerol, tocopherol, liquid paraffin, white vaseline, hydrogen chloride, and purified water.

FIGURE LEGENDS

Figure 1. The chemical structures of sorbic acid (**SA**) and its salt potassium sorbate (**PS**).

Figure 2. Patient no. 10 demonstrating (**A**) a positive patch test (++) on day 4 (D4) to "cremor cetomacrogolis" (CMC), a potassium sorbate (PS)/sorbic acid (SA)-containing cream base used to formulate compounded pharmaceutical corticosteroid creams (CPC), and (**B**) a positive patch test (+) on D4 to its vehicle component sorbic acid (SA) 2% eth.; SA 2% pet. as well as the other vehicle component cetearyl alcohol (20% pet.) remained negative.