Contact hypersensitivity to selected excipients of dermatological topical preparations and cosmetics in patients with chronic eczema

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ABSTRACT

Objective: 1) Assessment of the frequency of contact sensitization to selected excipients of dermatological topical preparations and cosmetics in patients with chronic eczema. 2) Detection of the sources of sensitization.

Methods: 1,927 patients with chronic eczema (mean age 44.3 years, 601 males, 1,326 females) were patch tested with selected excipients.

Results: The main rates of sensitization observed were: thiomersal 11.3%, wool alcohols 4.0%, phenylmercuric acetate 3.1%, formaldehyde 2.5%, dodecyl gallate 2.0%, Bronopol 1.9%, dibromodicyanobutane/phenoxyethanol (1:4) 1.7%, chloracetamide 1.6%, chlorhexidine digluconate 1.5%, Kathon CG 1.4%, parabens 1.1%, diazolidinyl urea 0.9%, imidazolidinyl urea 0.7%, benzalkonium chloride 0.7%, and Quaternium-15 (quaternary ammonium salt) 0.7%.

Conclusion: The rate of sensitization to the excipients included in dermatological topical preparations and cosmetics in patients with chronic eczema is significant. Complete information on all the ingredients is necessary

KEY WORDS

contact hypersensitivity, excipients, emulsifiers, antioxidants, preservatives

Introduction

In patients with chronic eczema it is necessary to take into account sensitization to a rather broad spectrum of contact allergens, including excipients included in dermatological topical medications and cosmetics. Positive patch tests support the diagnosis of contact hypersensitivity (1–9).

Material and methods

A total of 1,927 patients (mean age 44.3 years) – 601 men (mean age 44.5 years) and 1,326 women (mean age 44.2 years) – with chronic eczema were enrolled in the study from 2001 to 2006. The majority of patients were between 41 and 50 years old. In 738 patients the basic diagnosis was atopic eczema, with a mean age of 37.3

Table 1. Tested excipients, their concentrations, and vehicles; pet-petrolatum.

Group, subgroup, allergen c/v
preservatives
derivatives of p-hydroxybenzoic acid
paraben-mix 16% pet.
formaldehyde and formaldehyde-releasing preservatives
formaldehyde 1% aqua
Bronopol 0.5% pet.
quaternium-15 1% pet.
imidazolidinyl urea 2% pet. (Germal 115)
diazolidinyl urea 2% pet. (Germal II)
DMDM hydantoin 2% aqua
izothiazoline derivatives
Kathon CG 0.01% aqua
organic compounds of mercury
thiomersal 0.1% pet.
phenylmercuric acetate 0.05% pet.
quarter ammonium bases
benzalkonium chloride 0.1% pet.
diquanides
chlorhexidine diglocunate 0.5% aqua
others
phenoxyethanol 1% pet.
dibromodicyanobutane/phenoxyethanol (1:4) 1% pet.
chloracetamide 0.2% pet.
chlorocresol 0.2% vaz.
sorbic acid 2% pet.
triclosan 2% pet.
glutar(di)aldehyd 0.3% pet.
dichlorophene 0.5% pet.
chloroquinaldol 5% pet.
antioxidants
propyl gallate 0.5% pet.
dodecyl gallate 0.3% pet.
butylhydroxyanisole (BHA) 2% pet.
butylhydroxytoluene (BHT) 2% pet.
emulsifiers
wool alcohols 30% pet.
propyleneglycol 5% pet.
triethanolamine 2.5% pet.

years. Most patients with atopic eczema were 21 to 30 years old.

The inclusion criterion was eczema with a duration of at least 1 year; the mean duration at the time of enrollment was 3.7 years without remission. In the subgroup of patients with atopic dermatitis the duration was 5 years and in the non-atopic patients it was 2.9 years (many patients had several eczema flare-ups, but the duration of these flares was not taken into account when assessing the overall duration of eczema). The patients were patch tested and the clinical and anamnestic data were recorded.

The tested excipients (Hermal, Reinbeck, Germany), their concentrations, and the vehicles used are summarized in Table 1. The excipients were separated into preservatives, emulsifiers, and antioxidants.

The patch tests (Curatest®, Lohman & Rauscher, Rengsdorf, Germany) were applied for 48 hours, and the skin reactions were evaluated after 72 and 96 hours.

Results

The frequency and percentage of allergic reactions are listed in Table 2 for the entire group of patients. The peak of allergic reaction was generally attained after 72 hours, whereas in Kathon CG, thimerosal, gallates, and wool alcohols this was after 6 hours. The most significant differences in the frequency of sensitization between men and women were detected in dibromodicyanobutane/phenoxyethanol: in women this reached 2.1%, whereas in men it was only 0.8%. Sensitization to Kathon CG was significantly higher in women (1.8%) compared to men (0.3%). Sensitization to imidazolidinyl urea was also higher in women (1%) compared to men (0.3%). Comparing the frequency of sensitization to adjuvant substances between the subgroups of patients with and without atopic eczema revealed a higher frequency of sensitization to Bronopol (2.5%) in the atopic subgroup, compared with 1.6% in the non-atopic subgroup. Slightly higher sensitization to Kathon CG was found in the subgroup of patients with atopic eczema (1.8%), compared with 1.1% in patients without atopic eczema. An interesting finding is the detection of higher frequency of sensitization to parabens in the subgroup of patients without atopic dermatitis (1.6%) compared with the subgroup with atopic dermatitis (0.4%); similarly, sensitization to wool alcohols was higher in patients without an atopic history (4.8%) compared with 2.7% in patients with an atopic history.

Our 1,927 patients were using 3,950 cosmetic products and 411 dermatological topical preparations at the time of examination.

Discussion

Derivatives of p-hydroxybenzoic acid

Parabens are derivatives of p-hydroxy-benzoic acid. Methyl-, ethyl-, propyl-, butyl-, isobutyl-, and isopropylester are used. They are used as preservatives in both dermatological and cosmetic products. Sensitization in the Czech Republic reached 1.4% in 2006.* Some authors found positive tests in 0.6% of 8,212 patients with eczema (1983–1996) (10), compared to 1.5% in 664 patients with

eczema at a later period (11). The sensitization potential of parabens is not high considering its long-term use. In Belgium between 1987 and 1997 in 8,521 patients it was 0.8% (1), in 11 European countries from 1999 to 2000 0.5% (6), in Great Britain from 2004 to 2005 in 6,958 patients it was 0.8% (5). In our eczema patients investigated between 2001 and 2006 it was 1.1%.

Formaldehyde and formaldehyde-releasing preservatives

Contact hypersensitivity to formaldehyde was found in 48 patients (2.5%). Preservatives releasing formaldehyde, which were the objects of our interest, involve Bronopol (2-brom-2-nitro-propandiol), imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin (dimethylol-dimethylhydantoin), and Quaternium-15 (N-3-chloroallyl hexaminium chloride).

A patient may be sensitized either to the excipient or to formaldehyde, but also to both. Cross-sensitization to other preservatives releasing formaldehyde is also possible. In this group of preservatives sensitization to Bronopol, which is used in cosmetics, was observed in 37 cases. In previous studies, sensitization to Bronopol was reported as 0.4 to 2.6% (12–14).

Goosens et al. (1997) found sensitization to diazolidinyl urea in patients with chronic eczema in 0.3% and to imidazolidinyl urea in 0.17% (1). Pecquet found sensitization to diazolidinyl urea in 0.9% and to imidazolidinyl urea in 0.5% (15). In Great Britain, Jong et al. found sensitization to diazolidinyl urea in 1.1% and to imidazolidinyl urea in 0.9% (5). In our patients we found a sensitization to diazolidinyl urea in 0.9% and to imidazolidinyl urea in 0.7% (5).

Cross-sensitivity between diazolidinyl urea and imidazolidinyl urea is frequent (16). According to NACDG (North American Contact Dermatitis group), sensitization to DMDM hydantoin is reported at 1.9 to 2.6% (16), or in 0.04% reported by Goosens (1), whereas in our patients it was 0.5%.

Quaternium-15 is used not only as preservative in cosmetics but also in other products (e.g., varnishes, glues, and inks). In Europe, sensitization to Quaternium-15 ranges from 1% to 3% of sensitized patients. In the Czech Republic it represented 0.8% in 2006* and in North America it is about 9% (16). In the period between 1997 and 1999 one group of authors found contact hypersensitivity to this preservative only in 0.2% (11); in Great Britain it was 1.9% from 2004 to 2005 (5), whereas we noted a rate of 0.7% from 2001 to 2007.

Some of the patients may be also sensitized to formaldehyde (about 50%). Reactions to other preservatives that release formaldehyde range from 3% to 6%. Quaternium-15 seems to be the strongest allergen among formaldehyde-releasing preservatives. It has been used as a preservative in European countries less frequently than in North America (16–19).

Izothiazoline derivatives

Kathon CG is a mixture of isothiazoline derivatives (5-chloro-2-methyl-4-izothiazolinon and 2-methyl-4-izothiazolinon 3:1). It is a preservative frequently used in the cosmetics industry. Sensitization to Kathon CG in patients with eczema ranges from 0.9% to 6.1% (1, 10, 12, 18–27). The sensitization rate in the Czech Republic in 2006 was 2.2%.*

A positive reaction to Kathon CG may also signalize cross-sensitivity with isothiazolin derivatives like benzothiazolinone and octylizothiazolinone, used for preserving industrial fluids.

Organic mercury compounds

In our patients, sensitization to thimerosal (Mertiolate) was frequent (11.3%). It is characterized by a relatively high sensitizing potential (1.3–2% and more) (1). Novák et al. studied it over a period of 20 years (28).

Sensitization to phenylmercuric acetate was relatively frequent (3.1%). In our opinion, hypersensitivity to phenylmercuric acetate may be the consequence of cross-sensitivity to thimerosal.

Quarternary ammonium bases

Benzalkonium chloride is one of the quarternary ammonium bases. It is utilized as a preservative in cosmetics and quite widely in the pharmaceutical industry; for example, for the preservation of eye drops and ointments as well as in solutions used for contact lenses storage. Sensitization is rare (1, 15, 16). Goosens reported a sensitization in 0.02% (1); in our patients it was 0.7%.

Diquanides

In evaluating patch tests with chlorhexidine, irritant reactions should be distinguished. Phenoxyethanol is used as a preservative in cosmetic and pharmaceutical products. It is a component of the preservative Euxyl K 400, which is a mixture of dibromodicyanobutane/phenoxyethanol 1:4; it is used in cosmetics as well as in other industry branches. Dibromodicyanobutane has a higher sensitizing potential. The frequency of sensitization is reported to be low. Goosens reports 0.3% from 1985 to 1997 (1), Wilkinson et al. 3.5% from 1999 to 2000 in 11 European countries (6), and Jong et al. 1.1% in Great Britain from 2004 to 2005 (5) In our patients between 2001 and 2006 it was 1.7%.

**Data from the dermatoallergology section of the Czech Dermatovenerological Society*

Table 3. Comparison of the frequency of sensitization to selected excipients as observed in various countries.

Group, subgroup, allergen	I.DVK 2001–06 *n* = 1,927	Belgium 1985–97 *n*= 8,521	Europe 1999–00 11 countries	UK 2004–05 *n* = 6,958
preservatives				
derivates of p-hydroxybenzoic acid				
paraben-mix	1.1	0.8	0.5	0.8
formaldehyde and formaldehyde-releasing preservatives				
formaldehyde	1.1	0.8	0.5	0.8
Bronopol	2.5	0.9	2.0	2.0
quaternium-15	1.9			1.3
imidazolidinyl urea (germal 115)	0.7	0.4	1.0	1.9
diazolidinyl urea (Germal II)	0.7	0.2	1.0	0.9
DMDM Hydantoin	0.9	0.2	0.5–1.5	1.1
izothiazoline derivates				
Kathon CG	1.4	1.5	2.5	
organic compounds of mercury				
thiomersal	11.3	1.6		
phenylmercuric acetate	3.1			
quarter ammonium bases				
benzalkonium chloride	0.7	0.02		
diquanides				
chlorhexidine diglocunate (in water)	1.5	0.3		
others				
phenoxyethanol	0.3	0.1		
dibromodicyanobutane/phenoxyethanol (1:4)	1.7	0.3	3.5	1.1
chloracetamide	1.6	0.2		
chlorocresol	0.3	0.2		0.4
sorbic acid	0.2			
triclosan	0.5	0.1		
glutar(di)aldehyd	0.5	0.3		
dichlorophene	0.4			
chloroquinaldol	0.3			
antioxidants				
propyl gallate	0.3			
dodecyl gallate	2.0			
butylhydroxyanisole (BHA)	0.5			
butylhydroxytoluene (BHT)	0.1			
emulsifiers				
wool alcohols	4.0			
propyleneglycol	0.2			
triethanolamine	0.5			

I. DVK: First dermatovenereological department, St. Anne Hospital, Brno

Others preservatives

Contact hypersensitivity to chloracetamide has been estimated between 0.25 and 1.5% (1, 16). Goosens et al. (1997) found sensitization to chloracetamide to be 0.2% in 8,521 patients with eczema (1).

Chlorocresol is tested at a concentration of 1%. It is used as preservative in pharmaceutical preparations as well as in cosmetics, glues, paints, coating compounds, textile finishes, and cooling fluids in the metal industry. Sensitization to chlorocresol is rare. Goosens reports 0.2% (1), and in our patients between 2001 and 2006 it was 0.3%.

Sorbic acid is used as a preservative in the pharmaceutical industry, often in combination with parabens, as well as in food and other industries. The frequency of sensitization ranges from 0.3% to 1.4% (16).

Triclosan is used as a preservative in the pharmaceutical and cosmetic industries, for preserving cutting oils, emulsions, and so on. Sensitization is reported to be 0.5% (16).

Glutar(di)aldehyde may be present in hair-care products, mouthwashes, and toothpastes. It can be also present in medicines, disinfectants, and technical prod-

ucts such as dyes, developers, and so on. Cases of sensitization to glutar(di)aldehyde, particularly in nursing staff, due to disinfectants have been described. Cross-sensitivity with formaldehyde is possible (16).

Dichlorophen may be found in some pharmaceutical and cosmetic preparations, and it is also used in other industries (e.g., cutting oils, cooling emulsions, and agrochemicals). Reports on contact hypersensitivity are sporadic (16).

Chloroquinaldol may be present in pharmaceutical preparations (16).

Antioxidants

Propyl gallate (propylester of 3,4,5-trihydroxy-benzoic acid) is used in pharmaceutical and cosmetic products and also in the food industry (E 310). It is also used as preservative. In 1,460 patients with chronic eczema examined at our clinic, sensitization to propyl gallate was 1.9% from 1989 to 1996 (10, 29).

Dodecyl gallate has similar properties and also affects the skin. Cross-sensitivity among gallates may occur. The sensitizing potential increases with the chain length, so dodecyl gallate is a stronger sensitizer. Simultaneous sensitization to propyl gallate and dodecyl gallate was not demonstrated by our group.

Butylhydroxianisole (BHA) (E 320) and butyl hydroxitoluene (BHT) (E 321) are used as stabilizers in food, pharmaceutical, and cosmetic products. Both have also preservative effects. The prevalence of sensitization to BHA and BHT is low (0.2–0.7%). Cross-sensitivity between BHA and BHT is frequent (16).

Emulsifiers

From the dermatological point of view, wool alcohols are the most important. They may be components of topical medications as well as of cosmetics, but they are used in the industrial setting. Contact hypersensitivity also to wool alcohols is seen frequently in patients with chronic venous insufficiency accompanied by stasis dermatitis. It is gradually increasing and has been reported to range from 1.0% to 4.3% (14, 18, 19, 26, 30–33). In the Czech Republic it was 1.8% in 2006.* In 8,212 patients with eczema examined at our clinic from 1983 to 1996 it reached 1.5% (10), and 4.4% in 664 patients from 1997 to 1999 (11).

Propyleneglycol is used abundantly both in the pharmaceutical and cosmetic industries as well as in the technical sector. In addition to emulsifying properties, it is also a preservative, mollifying, and hygroscopic substance. Used mainly in cosmetics, it causes irritation rather than sensitization, although sensitization is possible. The sensitization frequency is reported to range from 0.1% to 4.1% (34, 35). Novák et al. (2000) observed sensitization to propyleneglycol in 0.8% of cases. The frequency of sensitization at our clinic in 1,310 patients with eczema was 2.6% from 1989 to 1996 (10).

Triethanolamine is used in the same way as propyleneglycol and it has similar effects on the skin (irritating rather than sensitizing). It sensitizes only rarely, but cross-sensitivity with diethanolamine and monoethanolamine may occur (16).

Observations

There was no difference in the rate of contact sensitization to excipients between the atopic and non-atopic patients.

In the Czech Republic sensitization to further excipients was not studied systematically; thus a comparison of contact hypersensitivity as observed in other European countries is not available. Based on the results of this study, the developmental trends of sensitization in the Czech Republic can be predicted both for dermatological topical preparations and cosmetics.

Conclusion

The sensitization rates to the excipients in dermatological topical preparations and cosmetics in patients with chronic eczema are reported. Such a sensitization may be lasting or appear in flares. Extensive information on all the ingredients of pharmaceutical and cosmetic preparations, including the excipients, is therefore necessary. Special care is to be paid to excipients.

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