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Allergic contact dermatitis to topical medicaments: Revisited

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Abstract

Background: Allergic reaction to topical drugs varies depending on use and availability of topical drugs and self-medication.

Objectives: We aimed to determine the incidence of contact dermatitis to topical medicaments among patients referred for patch testing

Methods: All patients with suspected allergic contact dermatitis were patch tested with standard and medicament series. The characterization was performed according to the MOAHLFA index

Results: 59/215 (27.4%) patients had positive reactions to at least 1 medicament but only 13/59 (22.0%) had a relevant history. The 3 most common positive medicaments were framycetin 23/215 (10.7%), miconazole 22/215 (10.2%), and econazole 17/215 (7.9%). Among those positive to medicament, face was the most common location 22/59 (37.3%). 39/215 (18.1%) had more than 2 co-positive standard allergens and showed significant higher rate of topical medicament sensitization. The contributing factors of medicament allergy were the history of suspected allergens in personal care products (OR = 2.09, P = 0.038), topical drugs (OR = 2.93, P = 0.002), topical treatment (OR = 2.47, P = 0.011), and history of drug allergy (OR = 1.78, P = 0.023).

Conclusion: The study showed a high rate of medicament sensitization especially antibiotic and antifungal drugs. The incidence of positive medicament patch test result was associated with facial dermatitis. Polysensitization and history of previous exposure, either as treatment or overusing of drugs, significantly associated with medicament positive patients. This study supports the inclusion of medicaments within the standard series of patch test.

Key words: allergic contact dermatitis, topical medicaments, patch test, contact sensitization, contributing factors

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Introduction

Allergic contact dermatitis is an inflammatory reaction due to expose with exogenous allergen and responds by delayed type hypersensitivity. The incidence of allergic contact dermatitis to topical medicament varies in each country. The contributing factors can be age, race, area of involvement, underlying diseases, accessibility to drugs and prescriptions together with self-medication habits of the population.[1-4] The rate of topical medicament sensitization in South East Asian contact dermatitis patients was last reported in 1989 at overall 22.5%.[1] Medication including topical drugs is loosely regulated and can easily be purchased over the counter in Thailand. Most patients still prefer to buy drugs directly from a pharmacy over obtaining prescription from a doctor. Owing to the self-medication habit of the population, a variety of "one cream treats all" formulations are available containing corticosteroid, antibiotics and/or antifungal agents. The exposure to such medicaments may induce contact sensitization. We aimed to determine the recent incidence of contact dermatitis to topical medicaments among patients referred for patch testing.

Materials and Methods

We conducted a prospective study in a tertiary referral medical center over a period of 1 year from 1st June 2014 to 31st May 2015. The study was approved by the Institutional Review Board of Royal Thai Army Medical Department (IRBRTA

322/2557). Patients who were suspected to have allergic contact dermatitis to allergens such as personal care products and topical drugs aged at least 18 years old were recruited for patch testing with standard series and topical medicament series (**table S1**). The exclusion criteria comprised of pregnancy, underlying diseases of immune abnormality e.g. human immunodeficiency virus positive or lupus erythematosus, and history of severe allergic reaction i.e. anaphylaxis. Patch test results were read at 72 hours and 96 hours with an extension up to 7 days in some patients in case of delayed patch test reaction, e.g. patients who had negative result to aminoglycoside.[5] Readings were in accordance with standard ICDRG readings were scored as -, ?+, +, ++, or +++. Only + reaction or more were regarded as true positive.[5] The patients were informed regarding the process of patch testing and signed consent forms.

Data collection

Demographic data including age, sex, occupation and history of atopic eczema, duration of symptoms, affected area of the rash, suspected allergens by history from patients, history of previous treatment and medications were recorded. The characterization was performed according to the MOAHLFA index (including Male, Occupation, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis, Aged 40 years and above) and other suspected contributing factors.[6]

Statistical analysis

Statistical analysis was performed by SPSS (version 17.0.2, 2009; SPSS Inc., Chicago, IL, USA). The Chi-square test was used to test for any significant difference between rate of medicament patch test positive and the patch test negative group, $p \leq 0.05$ was considered statistically significant.

Results

Two hundred and fifteen patients (male 48, female 167) were recruited for patch testing. The median age was 45 years old. Fifty-nine patients (27.4%) had positive patch test reaction to at least 1 medicament and 13 of these patients (22%) had a relevant history. Nine patients showed co-sensitization to 2 allergens of medicament series and 11 patients showed positive results to more than 2 allergens. The 5 most common positive medicament allergens were framycetin 23/215 (10.7%), miconazole 22/215 (10.2%), econazole 17/215 (7.9%), caine mixes 11/215 (5.1%) and neomycin 6/215 (2.8%) (**figure 1**).

Females were predominant amongst the medicament allergy group (79.7%), the mean age was 47 years, median onset of the rashes was 9 months and the most common location was the face 80/215 (37.3%). The demographic data was shown in **table 1**, however no statistical significance was found between the positive and negative medicaments groups. All 215 patients also had patch testing with the standard series, and 126 (58.6%) showed at least 1 positive standard allergen. Thirty-one patients (14.4%) had 2 positive allergens. Thirty-nine patients (18.1%) had more than 2 positive reactions and also showed a statistically significant higher rate of medicament sensitization ($p = 0.016$). The rate of positive patch test reaction to standard allergens, upon comparison between the positive and negative medicament groups, was shown in **figure 2**. The most common positive standard allergens in medicament positive group were nickel (4.2%) followed by fragrance mix I (4.1%) whilst the medicament negative group found positive reaction to nickel (14%), MCI/MI 11.5% and PPD 8%. Moreover, patients with positive reactions to allergens in the fragrance groups (fragrance mix I, fragrance mix II, and Balsam of Peru) were significantly found to be in concurrent

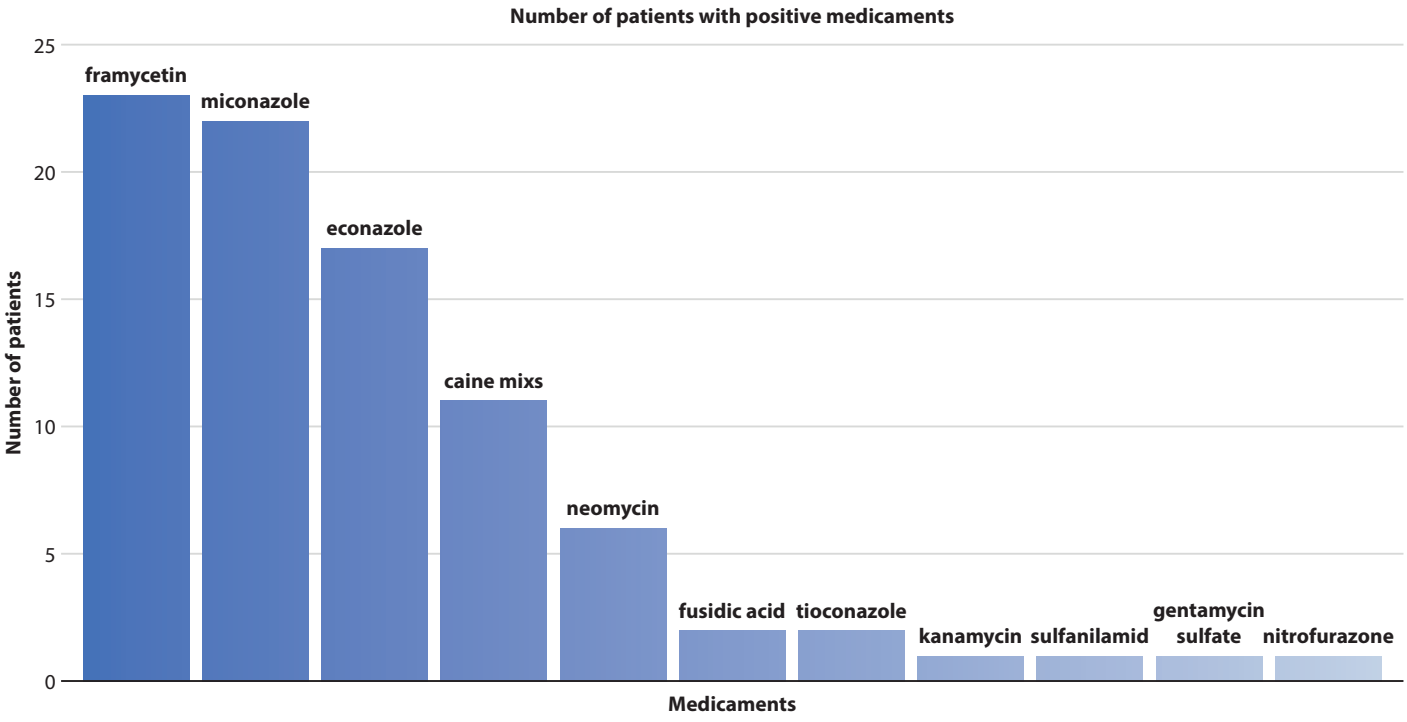

Figure 1. Number of patients with positive medicaments.

Table 1. Demographic data of all patients positive and negative to medicament series

Demographic data	Patients (N = 215)	Patients with Positive Medicament series (N = 59)	Patients with Negative Medicament series (N = 156)	*P*-value *
Sex				
Male	48 (22.3%)	12 (20.3%)	36 (23%)	0.717
Female	167 (77.6%)	47 (79.6%)	120 (76.9%)	0.717
Mean age (years)	45	47	44	0.298
Median duration of the rash (month)	8 (2-24)	9 (2-36)	7.5(2-24)	0.275
Area of rash				
Scalp	8 (3.7%)	1 (1.7%)	7 (4.5%)	0.451
Face	68 (31.6%)	22 (37.3%)	46 (29.5%)	0.324
Neck	5 (2.3%)	3 (5.1%)	2 (1.3%)	0.128
Trunk	22 (10.2%)	6 (10.2%)	16 (10.3%)	1.000
Upper extremities	6 (2.8%)	1 (1.7%)	5 (3.2%)	1.000
Lower extremities	17 (7.9%)	6 (10.2%)	11 (70.5%)	0.571
Hands	37 (17.2%)	8 (13.6%)	29 (18.5%)	0.426
Feet	8 (3.7%)	3 (5.1%)	5 (3.2%)	0.687
All over	44 (20.5%)	10 (16.9%)	34 (21.8%)	0.570

Data are presented as n (%); * $p < 0.05$

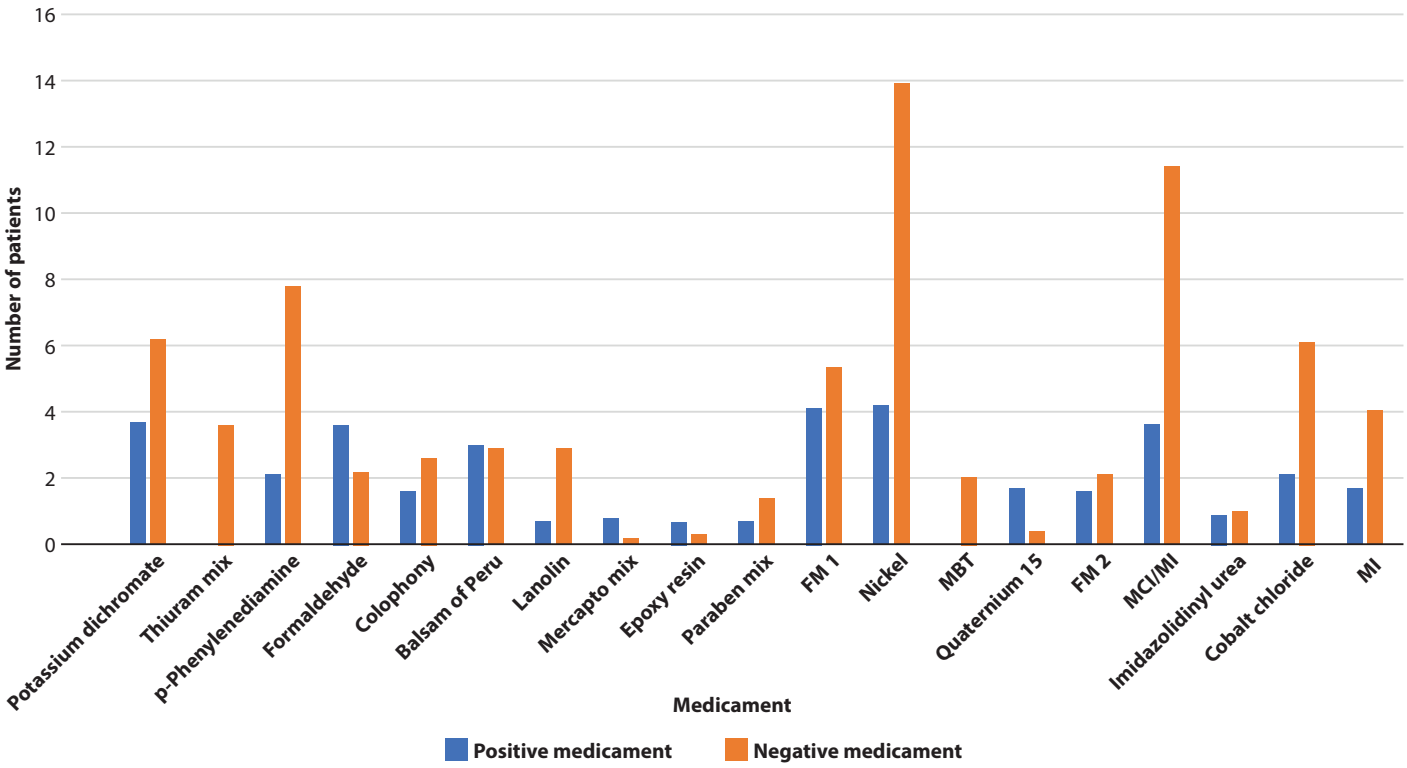

Figure 2. Rate of positive patch test reaction to standard allergens.

with positive medicament patch test (p = 0.008, **table S2**). Co-sensitization was found in more than one third of the medicament patch test positive patients (**table S3**).

Upon comparison between the medicament positive and negative group according to the MOAHLFA index (**table 2**). Statistical significances were seen between Framycetin and facial dermatitis (p = 0.031), Econazole and older age (p = 0.009), together with caine mixed and longer duration of rashes (p = 0.005).

Other contributing factors showing a statistically significant association with positive medicament patch tests were having history of suspected allergens in personal care products and topical drugs (p = 0.038 and p = 0.002, respectively), history of any systemic drug allergy (p = 0.023), history of topical treatment (p = 0.011) and history of using combined topical corticosteroids and anti-fungal drugs (p = 0.010) (**table 3**).

Chronological studies of medicament sensitization were shown in **table 4**.

Table 2. Comparison between the positive and negative medicament patch test according to the MOAHLFA index together with selected drug allergen.

	Positive medicament patch test (n = 59)	Negative medicament patch test (n = 156)	*p*-value*
Male	12 (20.3%)	36 (23.1%)	0.667
Occupational dermatosis	3 (5.1%)	5 (3.2%)	0.687
Atopic dermatitis	3 (5.1%)	7 (4.5%)	1.000
Hand eczema	8 (13.6%)	29 (18.5%)	0.426
Leg dermatitis	6 (10.2%)	11 (7.1%)	0.571
Face dermatitis	22 (37.3%)	45 (28.8%)	0.251
Age > 40 years	39 (66.1%)	81 (51.9%)	0.067
Duration (mo.) of the rash (median[IQR])	9 (2, 36)	7.5 (2, 24)	0.206

Data are presented as n (%); * $p < 0.05$

Table 3. Contributing factors in association with positive medicament patch test

	Positive medicament Series (n = 59)	Negative medicament Series (n = 156)	*p*-value*
History of systemic drug allergy			
Yes	13 (22%)	13 (8.3%)	0.023*
No	46 (77.9%)	143 (91.7%)	
Name of systemic drug allergy			
Penicillin	4 (6.67%)	6 (3.87%)	0.467
Sulfa	4 (6.67%)	2 (1.29%)	0.049
History of previous treatment			
Yes	53 (89.8%)	115 (73.7%)	0.011*
No	6 (10.2%)	41 (26.3%)	
Topical drug treatment			
None	6 (10.2%)	41 (26.3%)	0.011*
Steroid	33 (55.9%)	78 (50%)	0.437
Antifungal	8 (13.6%)	11 (7.1%)	0.134
Antifungal with steroid	8 (13.6%)	6 (3.8%)	0.010*
Antibiotic	2 (3.4%)	2 (1.3%)	0.307

Table 3. (Continued)

	Positive medicament Series (n = 59)	Negative medicament Series (n = 156)	*p*-value*
History of contact dermatitis (allergen)			
Personal care products	6 (10.2%)	5 (3.2%)	0.038 *
Topical drugs	6 (10.2%)	2 (1.3%)	0.002*
Household chemicals	6 (10.2%)	17 (10.9%)	0.878
Other	3 (5.1%)	8 (5.1%)	0.990

Data are presented as n (%); * $p < 0.05$

Table 4. Chronological studies of medicament sensitization

Study	Country	Population	Common positive Medicament	Most common location	Common positive standard allergen*
Goh et al.[1] 1989	Singapore	Contact dermatitis	Total 22.5% Neomycin 7.8% Proflavin 7.1%	Upper and lower extremity	Colophony 3.3%
Green et al.[2] 2007	UK	Contact dermatitis	Total 20.6% Neomycin 13.8% Gentamicin 6.6% *age > 70 years	Upper extremity	FM I 12.9% Myroxylon pereirae 8.1% Lanolin 4.5% *age > 70 years
Padua et al.[7] 2007	Germany	Contact dermatitis	Framycetin 4.9% Gentamicin 3.3%	N/A	N/A
This study	Thailand	Contact dermatitis	Framycetin 10.7% Miconazole 10.2%	Face	Nickel 18.2% MCI/MI 15% FM I 9.6%

* over all patient

Discussion

Goh et al. reported a high positive rate of medicament allergy at 22.5% in Singapore patients.[1] Similar to Green et al. from the United Kingdom, who also identified topical medicament allergy at 20.6%.[2] Our study found a slightly higher rate at 59/215 (27.4%) of patients with positive patch test reactions to at least 1 medicament. Once the relevance history was taken into consideration, the true rate of the relevance positive patch test was 13/59 (22.0%). The relevance history of the positive patch test was somewhat difficult to establish as the sensitization might have occurred several years ago. We also found the co-sensitization among different drugs in the same group with similar chemical structure which might contribute to the low rate of true relevance positive patch test. We would suggest a careful history taking of previous medicament exposure.

The demographic data of this study did not show significant differences between the medicament patch test positive and negative groups. Goh et al. and Green, et al. noted that contact sensitization to topical medicaments was common in advancing age due to the frequent use of topical medicaments and having longer exposure to various allergens.[1,2] Many studies identified leg dermatitis and leg ulcer as influences on the propensity to develop a medicament allergy and the rate of sensitization increased with duration of the ulcer.[1,3,8] Our study showed facial dermatitis as the most common clinical presentation, 3 times more than leg dermatitis in medicament positive group. In our hospital, leg ulcers and venous stasis of the legs were mainly referred to the surgery department. Only a few patients with leg dermatitis were referred to the dermatology division. Previous study found the association between atopic dermatitis and topical medicament allergy in children.[9] Our study, despite the inclusion criteria of ≥ 18 years old, did not show any different between the medicament positive and negative groups in patients with atopic dermatitis as shown in the MOAHLFA index.

The antibiotics group was the most common positive medicament allergens.[7,10] Framycetin was known as a common positive medicament patch test in association with leg dermatitis and leg ulcer for 5 decades.[11,12] In our study, framycetin showed a rather high rate of positive medicament patch test at 10.7% in comparison to a previous study from Germany at 4.9%.[7] Neomycin was our second most frequent positive medicament patch test at 2.8%. Framycetin and neomycin are aminoglycoside antibiotics that have closely related chemical structures. Cross-reaction among these 2 medicaments is quite frequent.[13] Previous studies found the positive rate of 7.8% and 12.8% in Singapore and United Kingdom respectively.[1-2] Another study from Canada reported a different most common positive patch test antibiotics i.e. bacitracin.[10]

Antifungal medicament allergy in our study is particularly high. Imidazoles were the most frequently prescribed topical antifungal drugs. Our study found miconazole was the most

common positive patch test antifungal agent at 10.2%, followed by econazole at 7.9%. In our hospital econazole was an imidazole derivative used in combination with corticosteroid, Ecosone™. The combination drug was commonly prescribed to most patients with chronic paronychia. Upon correlation with our results, patients with a positive patch test to econazole were older than the negative group. However, the discrepancy might be explained by cross-sensitization within the same imidazole groups.[14,15]

Local anesthetics derived from caines are widely used not only in injectable preparations, but also in topical forms such as creams used for pruritus ani, hemorrhoids, sunburn relief and anesthetic eye or ear drops. Our study found the rate of contact sensitization to caine mixes was 5.1% which was the same as a previous report of 4.0%.[16]

Allergy to other agents such as cetostearyl alcohol may present as either medicament or cosmetic allergy or both. They are beyond the scope of this article.

The increasing number of positive patch tests to standard allergens also increased the number of topical medicament allergens among our patients. Regarding the co-sensitization, only fragrances showed a significantly increased rate of co-positive reaction to medicaments when compared with other standard allergens. Polysensitization, 3 or more contact allergies, is associated with increased sensitization to further allergens including weak sensitizers such as paraben mix, wool alcohols and neomycin.[17,18] Many studies suggested the predisposing factors for polysensitization i.e. strong patch-test reactions, genetic factors, environment exposure, allergens in combination and concomitant skin diseases.[17] Polysensitization could be one of the influent factors for medicament allergy. As a result, we suggested to discourage the overuse of topical medicament especially in polysensitized patients. Moreover, the positive medicament patients in our study significantly had a history of systemic drug allergy, which might support a genetic factor hypothesis.

We believe the discrepancy of our results from other areas of the world in terms of contact sensitizing medicament can be explained by the fact that most medication can be obtained without any prescription in Thailand and many South East Asian countries. Moreover, most people in Thailand prefer to try some drugs before getting a prescription, i.e. self-medication.

Our study showed other contributing factors associated with medicament allergy i.e. history of previous treatment, history of using topical combination drugs (corticosteroids, anti-fungal agents and/or antibiotics), and history of allergy to personal care products or topical drug. The need for primary exposure to allergens was an obvious explanation to associate medicament allergy with history of previous treatment and history of allergy to personal care products or topical drugs. Furthermore, polysensitization could also play a role. Interestingly, our data associated medicament allergy only with history of using topical combination drugs but not the single drug therapy. The result emphasized the need to encourage the general public to obtain proper prescriptions. Self-medication with combination drugs might lead to exposure of unnecessary drugs and potential sensitization.

This study was performed in a monocenter, which had a limited number of patients recruited into the study. The relevance of medicament sensitization was difficult to establish due to various unknown source of allergens e.g. herbal drugs and traditional medicine or the sensitization might have occurred many years ago.

Conclusion

The study showed a high rate of medicament sensitization among patients who required patch testing especially antibiotic and antifungal drugs. We found the incidence of positive medicament patch test result was not only associated with older age but also anatomical location of the skin lesion i.e. facial dermatitis according to the MOAHLFA index. Polysensitization and history of previous exposure, either as treatment or overusing of drugs, significantly associated with medicament positive patients. This study supports the inclusion of medicaments within the standard series of patch test.

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Conflicts of Interest

No conflict of interest

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Table S1. Standard and medicament patch test series

Standard patch test series	Conc.	Standard patch test series	Conc.
1. Potassium dichromate	0.25 pet	13. Nickel sulfate	2.5 pet
2. Neomycin sulfate	20.0 pet	14. Mercaptobenzothiazole	0.25 pet
3. Thiuram mix	1.0 pet	15. Quarternium 15	2.0 pet
4. p-Phenylenediamine	1.0 pet	16. Fragrance mix II	14.0 pet
5. Formaldehyde	2.0 aq	17. MCI/MI (Kathon CG)	0.01 aq
6. Colophony	20.0 pet	18. Imidazolidinyl urea	2.0 pet
7. Balsam of Peru	25.0 pet	19. Black rubber mix	0.6 pet
8. Lanolin alcohols	30.0 pet	20. Paraben mix	12.0 pet
9. Mercapto mix	1.0 pet	21. Cobalt chloride	1.0 pet
10. Epoxy resin	1.0 pet	22. Benzocaine	5.0 pet
11. 4-tert-Butylphenol formaldehyde resin	1.0 pet	23. Methylisothiazolinone	0.2 aq
12. Frangrance mix I	8.0 pet		
Medicament patch test series	**Conc.**	**Medicament patch test series**	**Conc.**
1. Chloramphenicol	5.0 pet	8. Framycetin sulfate	20.0 pet
2. Kanamycin sulfate	10.0 pet	9. Caine mix III	10.0 pet
3. Quinine sulfate	1.0 pet	10. Miconzaole	1.0 alc
4. Sulfanilamide	5.0 pet	11. Econazole	1.0 alc
5. Gentamicin sulfate	20.0 pet	12. Caine mix IV	10.0 pet
6. Nitrofurazone	1.0 pet	13. Fusidic acid sodium salt	2.0 pet
7. Bacitracin	5.0 pet	14. Tioconazole	1.0 pet

Table S2. Topical medicament concurrent with standard series allergy

Group of standard allergens	Concurrent with positive medicament patch test (n = 59)	Concurrent with negative medicament patch test (n = 156)	*P*-value*
Fragrances (n = 31)	15 (25.4%)	16 (10.3%)	0.008
Metals (n = 65)	18 (30.5%)	47 (30.1%)	1.000
Preservatives (n = 47)	18 (30.5%)	29 (18.6%)	0.066
Rubber (n = 7)	3 (5.1%)	4 (2.6%)	0.400

Data are presented as n (%); * $p < 0.05$

Table S3. Concomitant sensitization among medicament

Medicaments (N = positive patients)	Co-sensitization (N = positive patients)
Neomycin (6)	Kanamycin (1), Gentamicin (2), Framycetin (4), Miconazole (2), Econazole (4)
Kanamycin (1)	Kanamycin (1), Gentamicin (1), Framycetin (1)
Sulfanilamide (1)	Framycetin (1), Miconazole (1)
Gentamicin (3)	Neomycin (2), Kanamycin (1), Framycetin (2), Econazole (1)
Framycetin (23)	Neomycin (4), Kanamycin (1), Gentamicin (2), Miconazole (8), Econazole (7), Sulfanilamide (1), Caine mixes (1)
Caine mixes (12)	Framycetin (1), Miconazole (3), Fusidic acid (1)
Miconazole (22)	Neomycin (2), Econazole (8), Framycetin (8), Sulfanilamide (1), Caine mixes (3)
Econazole (17)	Kanamycin (4), Gentamicin (1), Framycetin (6), Miconazole (8)
Fusidic acid (3)	Caine mixes (1)

(n = positive patients)