

Cross-reactions to systemic corticosteroids in patients contact sensitized to budesonide

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Budesonide is a well-known contact sensitizer routinely patch tested in the baseline series of several countries. Prevalence of contact allergy to this corticosteroid ranges from 0.6% in Spain¹ to 0.8% in the European surveillance system on contact allergies.² Patients contact sensitized to budesonide typically develop only cutaneous reactions when this corticosteroid is administered systemically.³ Patients are difficult to manage, owing to the high frequency of cross-reactions not only among topical⁴ but also systemic corticosteroids (SCSs).⁵ In fact, patients previously contact sensitized to budesonide are at risk of systemic allergy caused by SCS,⁶ as described for patients with hydrocortisone hypersensitivity.⁷ Herein we present a study on patch tests with a series of SCS in patients with contact allergy to budesonide.

METHODS

Between January 2017 and December 2019 we collected data on 23 patients (female [F] 18, male [M] 5; mean age 57.3 years) referred for contact dermatitis due to budesonide and diagnosed by positive patch test (0.01% pet.). All 23 patients were patch tested with a series of 10 SCS frequently used in Italy belonging to the three groups of the Baeck classification system: hydrocortisone 21-sodium hemisuccinate, methylprednisolone, methylprednisolone sodium succinate, prednisone, triamcinolone (group 1); triamcinolone acetonide (group 2); and betamethasone sodium phosphate, dexamethasone, dexamethasone 21-disodium phosphate, and flucortolone (group 3).⁸ Ethanol solution test preparations with SCS (Sigma-Aldrich, Milan, Italy) were made in the Laboratory of Dermatology Section of the University of Perugia (Italy) at 0.1%.⁹ Micropipettes were used and 0.2 mL of SCS ethanol solutions were simultaneously occluded for 48 hours with Haye's Test

Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on SOFIX tape (Artsana, Grandate, Italy) and evaluated on day (D)2, D4, and D7.¹⁰ Control patch test with the 10 SCS ethanol solutions were performed in 20 healthy participants.

RESULTS

Among the 23 patients, 14 (60.9%) tested positive to at least one SCS (F 10, 71.4%; M 4, 44.4%; mean age 57.9 years), nine of them to all three groups of the Baeck classification⁸ (Table 1). Irritant or doubtful reactions were not observed. Patch tests were negative in the controls. The distribution of positive patch test results according to the classification of Baeck is shown in Table 2.

DISCUSSION

Cross-reactivity between budesonide and other corticosteroids, especially those topically administered, has been studied for a long time.⁴ In our case series the prevalence of positive patch test reaction to at least one SCS in patients with contact allergy to budesonide was 60.9%. A high percentage of patients showing positive reaction to all three Baeck groups was noted (64.3%), whereas three patients (21.4%) were positive to only one Baeck group. This confirms the hypothesis of two different types of corticosteroid-sensitized patients: the first (Profile 1) reacting to molecules from one unique group determined by SCS molecular charge, and the second (Profile 2) reacting to the entire spectrum of groups determined by SCS molecular structure.⁸

Budesonide is an equal mixture of S (Baeck group 1) and R (Baeck group 2) diastereoisomers, enabling it to cross-react within these two groups.^{11,12} In fact, in our patients, positive reactions to SCS were more

TABLE 1 Patch test results in budesonide-positive patients with at least one positive patch test reaction to systemic corticosteroids and group distribution according to the Baeck classification

Systemic corticosteroids ^a	Patient no. (gender, age)													
	1 (M, 84)	2 (F, 66)	3 (F, 75)	4 (M, 60)	7 (M, 39)	9 (F, 41)	11 (F, 32)	12 (M, 56)	13 (F, 56)	15 (F, 50)	16 (F, 59)	20 (F, 56)	22 (F, 71)	23 (F, 67)
Group 1														
Hydrocortisone 21-sodium hemisuccinate	+++	++	-	-	-	-	+++	-	+++	-	-	-	++	-
Methylprednisolone	-	++	++	-	-	-	++	+++ ^o	++	-	-	++	-	-
Methylprednisolone sodium succinate	++ ^o	+++ ^o	++	-	-	-	++	+++	-	-	++ ^o	-	-	++
Prednisone	-	++	++	-	-	-	+++ ^o	++	-	+++	-	-	-	-
Triamcinolone	-	+++	++	-	-	+++	++	+++	++	-	++	+++	-	-
Group 2														
Triamcinolone acetonide	+++	++	+++	++	++	+++	++	+++	++	++	+++	++	-	++
Group 3														
Betamethasone sodium phosphate	++	-	++	-	-	-	-	-	-	-	-	-	-	-
Dexamethasone	++	-	++	-	-	-	+++	++	++	-	-	+++	-	++
Dexamethasone 21-disodium phosphate	++ ^o	++	++	-	-	-	++	++	++	-	+++	-	-	-
Fluocortolone	++	-	+++ ^o	-	-	-	+++	++	+++ ^o	-	-	++	-	-
Group distribution	1, 2, 3	1, 2, 3	1, 2, 3	2	2	1, 2	1, 2, 3	1, 2, 3	1, 2, 3	1, 2	1, 2, 3	1, 2, 3	1	1, 2, 3

Note: Positive reactions at D7 (the others at D4).

Note: Patient number 5, 6, 8, 10, 14, 17, 18, 19, and 21: no positive reactions.

^aAll 0.1% in ethanol.

TABLE 2 Positive patch test results in 23 patients sensitized to budesonide according to the Baeck classification

Systemic corticosteroids	Number of positive reactions	Number of patch tests performed	%
Group 1	31	115	27.0
Hydrocortisone 21-sodium hemisuccinate, methylprednisolone			
Methylprednisolone sodium succinate, prednisone			
Triamcinolone			
Group 2	13	23	56.5
Triamcinolone acetonide			
Group 3	22	92	23.9
Betamethasone sodium phosphate, dexamethasone			
Dexamethasone 21-disodium phosphate, fluocortolone			

frequent in group 1 (27.0%) and group 2 (56.5%). The lower prevalence of positive reactions to SCS of group 3 (23.9%) is likely due to the small number of betamethasone sodium phosphate reactions, which caused positive reactions only in two patients (8.7%), suggesting a good tolerance of this SCS in patients with corticosteroid allergy.¹¹

By contrast, triamcinolone acetonide belonging to group 2 showed the highest prevalence of positive reactions (56.5%), confirming its potential cross-reactivity with budesonide.¹² Moreover, triamcinolone acetonide, frequently used as intralesional and intra-articular drug, resulted in positive reactions in two of the three monosensitized patients (numbers 4 and 7). This underlines the necessity to avoid the use of this SCS in patients contact sensitized to budesonide.

In conclusion, most patients contact sensitized to budesonide react to SCS belonging to any Baeck group; betamethasone sodium phosphate seems to show the best tolerance profile. Because budesonide is routinely tested in the baseline series, in case of a positive reaction, it is recommended to patch test an exhaustive series of these potentially lifesaving drugs to determine the individual sensitization/tolerance profile of patients.

CONFLICTS OF INTEREST

All authors have no interests to report.

AUTHOR CONTRIBUTIONS

Katharina Hansel: Conceptualization; formal analysis; investigation; methodology; supervision; validation; writing-original draft; writing-review and editing. **Rossella Marietti:** Data curation; formal analysis; investigation; methodology; visualization. **Leonardo Bianchi:** Data

curation; validation; writing-review and editing. **Marta Tramontana:** Data curation; validation; writing-review and editing. **Foti Caterina:** Supervision; writing-review and editing. **Paolo Romita:** Supervision; writing-review and editing. **Luca Stingeni:** Conceptualization; formal analysis; investigation; methodology; supervision; validation; writing-original draft; writing-review and editing.

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