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Contact Dermatitis and Allergy

Type-IV hypersensitivity to betamethasone valerate and clobetasol propionate: results of a multicentre study

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Summary

Background Most studies investigating steroid allergy have been performed with tixocortol pivalate, hydrocortisone butyrate and budesonide. Betnovate® and Dermovate® are widely prescribed in the U.K. but little is known about the frequency of sensitization to them.

Objectives To determine the optimum method to detect contact allergy to betamethasone valerate (BV) and clobetasol propionate (CP).

Methods Seven centres tested consecutive patients attending for investigation of suspected allergic contact dermatitis to these steroids at a range of concentrations in different vehicles.

Results Of 1562 patients tested, 16 (1%) reacted to either BV or CP. Ten patients (0·7%) reacted to BV and 13 (0·8%) to CP. Two patients of a further centre were included in analysis of dilutions and vehicles. Sixteen of a total of 25 reactions (64%) were identified with a 1% dilution in ethanol.

Conclusions Consideration should be given to adding BV and CP to a standard allergy series, given that both are frequently used in the treatment of eczema and that most patients sensitized to them are not identified with currently used markers of steroid allergy. If patch tests to BV and CP are initially negative, but an allergy is suspected, the patient should be further investigated. Further studies are required to identify the ideal patch test material.

Key words: allergic contact dermatitis, betamethasone valerate, clobetasol propionate, patch test method

Type IV hypersensitivity to topical steroid preparations has increasingly been recognized since the first report in 1959.[1,2] The reaction may be delayed or masked by continuous steroid use and therefore difficult to establish from the history. However, an unrecognized allergy may result in treatment failure or worsening of the skin condition.

The potent topical steroid betamethasone valerate (BV, Betnovate®, introduced in November 1963) and super-potent steroid clobetasol propionate (CP, Dermovate®, introduced in March 1973) are frequently used by hospital dermatologists, and usage is mirrored in general practice.[3] As the frequency of contact allergy to a given substance increases with the amount of exposure within a population,[4] allergy to BV and CP is to be expected. As their structure differs from that of tixocortol pivalate (TP) and budesonide, the markers of steroid allergy in the standard series, clinically relevant allergies to these steroids may go undetected.

The best dilution and vehicle for patch testing has been debated.[1,2,5–7] A 1% dilution of topical steroids in

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ethanol (eth) has previously been found to be the most sensitive, with the exception of budesonide and TP.[5,7] However, commercial suppliers provide BV and CP for patch testing only in petrolatum (pet), because of the superior stability of this formulation.

In 1999, members of the British Contact Dermatitis Group conducted a multicentre study to establish the frequency of positive patch test reactions to topical BV and CP, and also to confirm the concentration and vehicle most suitable for patch testing.

Subjects and methods

Eight contact dermatitis investigation units participated in this prospective multicentre study. The information was collected on a standardized study form. Consecutive patients were patch tested to a standard series containing TP 1% pet and budesonide 0·1% pet. Additionally, these patients were tested to dilutions of BV and CP: BV 1% and 0·12% pet (as supplied by Chemotechnique Diagnostics, Malmö, Sweden and Trolab, Hermal, Hamburg, Germany); BV 1% and 0·001% eth (Chemotechnique, and dilution thereof); CP 1% and 0·25% pet (Chemotechnique and Trolab); CP 1% and 0·001% eth (Chemotechnique, and dilution thereof). The patch tests were read at days 2 and 4 and interpreted as either irritant or allergic, with an assessment of current or past relevance. In order to characterize the study population, the MOAHL index for the trial period was listed per participating centre: percentage of patients male (M), with occupational eczema (O), atopy (A), hand eczema (H) and leg involvement (L).

Results

Of 1562 patients tested in seven centres, 17 reacted to BV or CP, which was reported as an allergic response in 16 (1%) patients (Table 1). One patient with an irritant response was excluded. The frequency of positive reactions at individual centres varied between 0·6% and 3·2%. Two additional patients with positive reactions from a further centre were included in the analysis of dilutions and vehicles, but excluded from the rest of the study, as information on the total number of patients tested was missing.

Sixteen patients had a reaction to either BV or CP (Table 2). Ten patients (0·7%) reacted to BV, 13 (0·8%) to CP and seven to both. Three of the 16 patients had a reaction to budesonide in the standard series and one of these also to TP. Three patients had weak positive reactions of unknown relevance, which clinically did not resemble a vasodilatory steroid effect, but a contact-allergic response.

The mean age was 58·7 years (range 25–85) and 10 patients were female (62·5%). Six patients (37·5%) were atopic. Topical steroid therapy had been used for between 6 months and several years, but an allergic reaction to this was suspected in only two patients.

In total, 18 patients were included in the analysis of dilutions and vehicles. Seven of the 11 patients (64%) with a reaction to BV reacted to 1% eth. Nine of 14 patients (64%) with a reaction to CP reacted to 1% eth.

Discussion

The average prevalence of allergy to BV or CP in seven centres of the British Contact Dermatitis Group was 1% (range 0·6–3·2%). Most of these patients (81%) would have been missed with a standard series containing only TP and budesonide. Cross-reaction patterns[8,9] of topical steroids demonstrate TP and budesonide to be in different groups than BV and CP, which can be explained by their different structure. Therefore, TP and budesonide can not be relied on to identify sensitivity to the fluorinated topical steroids Betnovate® or Dermovate®, and separate testing is needed. The allergy is rarely suspected clinically and without

Table 1. Total number of patients patch tested, number of positive reactions to betamethasone valerate and clobetasol propionate, and percentage of patients male (M), with occupational eczema (O), atopy (A), hand eczema (H) and leg involvement (L) listed per participating centre

	Tested	+ve	% +ve	% M	% O	% A	% H	% L
Dundee	93	3	3·2	41	20	27	22	9
Amersham	163	1	0·6	25	12	41	24	20
Leeds	235	2	0·8	37	15	44	38	17
Bristol	98	2	2·0	33	18	33	29	5
Oxford	86	2	2·3	33	8	39	43	13
Sheffield	389	3	0·8	33	18	47	33	3
Nottingham	498	3	0·6	42	15	34	35	11
TOTAL	1562	16	1·0					

Table 2. Patients' reactions on days 2 and 4 (e.g. –/+) to tixocortol pivalate, budesonide and different dilutions and vehicles of betamethasone valerate and clobetasol propionate, together with interpretation: a = allergic; c = current relevance, p = past relevance, d = unknown relevance. NT = not tested. Patients 1: Amersham; 2–4: Nottingham; 5, 6: Bristol; 7, 8: Oxford; 9, 10: Leeds; 11–13: Dundee (plus one irritant reaction); 14–16: Sheffield; *17, 18: Liverpool, included only in analysis of dilutions and vehicles*

			Betamethasone valerate					Clobetasol propionate				
	Tixocortol pivalate	Budesonide	1% pet	0·12% pet	1% eth	0·001% eth		1% pet	0·25% pet	1% eth	0·001% eth	
1	–/–	–/–	–/–	–/–	–/–	–/–		–/–	–/–	–/++	–/–	a,c
2	–/–	–/–	–/–	–/+	–/–	–/+	a,c	–/–	–/–	–/–	–/+	a,c
3	–/–	–/–	–/–	–/–	–/–	–/–		–/–	–/–	–/–	–/+	a,d
4	–/–	–/–	–/–	–/–	–/–	–/–		++/++	NT	++/++	–/–	a,c
5	–/–	–/–	–/–	–/–	–/–	–/–		+/+	+/+	+/+	–/–	a,p
6	–/–	–/–	–/–	–/–	–/–	–/–		–/+	–/–	–/–	–/–	a,c
7	+	+	–/–	–/(+/–)	–/–	–/–	a,p	–/–	–/+	–/+	–/+	a,p
8	–/–	–/–	–/–	–/–	–/–	–/–		–/–	(+/–)/+	–/–	(+/–)/+	a,c
9	–/–	–/–	–/–	–/–	–/+	–/–	a,c	–/–	–/–	–/–	–/–	
10	–/–	+/++	–/–	–/–	–/–	–/–		–/–	–/–	–/–	–/+	a,p
11	–/–	–/–	–/(+/–)	–/(+/–)	–/(+/–)	–/–	a,d	–/(+/–)	–/(+/–)	–/(+/–)	–/–	a,d
12	–/–	–/–	–/–	–/–	–/(+/–)	–/–	a,d	–/–	–/–	–/–	–/–	
13	–/–	–/–	–/–	–/–	–/(+/–)	–/–	a,d	–/–	–/–	–/–	–/–	
14	–/–	–/–	+/–	–/–	–/–	–/–	a,c	+/–	+/–	+/–	–/–	a,c
15	–/–	+/–	+/–	+/–	+/–	–/–	a,c	+/–	+/–	+/–	+/–	a,c
16	–/–	–/–	+/+	+/+	+/+	–/–	a,c	+/+	+/+	+/+	–/–	a,c
17	–/+++	–/+	–/+	–/+	–/+	–/–	*a*	–/+	–/+	–/+	–/–	*a*
18	–/+++	–/–	–/+	–/–	–/–	–/–	*a*	–/–	–/–	–/–	–/–	

routine screening would be missed frequently. In any centre, the choice of additional corticosteroids to test should reflect the usage of topical corticosteroid in the local catchment population.[3,4]

The best dilution for patch testing is still not known and is controversial.[5–7,10] A high concentration may suppress and delay a potential reaction because of the immunosuppressive effect, whereas a low concentration may not be sufficiently sensitive to identify relevant allergies. We compared a high with a low concentration, which has been reported to yield most positive reactions.[10] In our study, a 1% concentration of CP or BV identified 64% of positive reactions, whereas lower concentrations were less sensitive. This is in keeping with other previous findings.[5,7]

There is also debate about the most suitable vehicle for steroid patch testing. Studies found an increased sensitivity of patch tests when using ethanol as a base.[5,7] It was argued that ethanol was a better patch-testing vehicle for lipid-soluble steroids, whereas petrolatum was more suitable for TP, which is water-soluble.[1,2] Patch test reactions developed at earlier time-points with ethanol as a vehicle compared to petrolatum.[5] Another disadvantage of testing with petrolatum is the uneven distribution of the steroid in this vehicle.[11] Our study confirmed ethanol as the most sensitive vehicle for patch testing with BV and CP.

Commercial suppliers provide BV and CP for patch testing only in petrolatum, because of increased stability of this formulation.[10] Steroids in ethanol may have a short duration of stability;[6] however, storage of patch test solutions in ethanol does not affect patch test reactions.[12] There is evidence that the allergen is not the steroid itself, but a degradation product thereof.[4] In this case reduced stability of the patch testing solution would not adversely affect the sensitivity of the test.

Interpreting corticosteroid patch test reactions can be difficult. While the clinicians involved felt the reactions seen were allergic, the inclusion of doubtful (+/–) reactions may be open to question although later (day 7) readings may have been helpful. However, even if one excludes these from the analysis, allergy to BV and CP still occurred in 0·8% of individuals tested. For CP 1% eth detected most reactions (eight of 13) and for BV 1% pet was the most sensitive (five of seven). This would not alter our overall conclusions.

We conclude that type-IV hypersensitivity to BV and CP was a significant problem in our study population. A 1% dilution of BV or CP was most suitable for screening and the use of ethanol as a vehicle had benefit over the use of petrolatum. However, there was a high false negative rate with any one concentration and vehicle and if there is a clinical suspicion of allergy to BV or CP a dilutional series should be used or alternatively intradermal testing may have value.[13] Further studies are required to determine a more sensitive patch test material to investigate suspected contact allergy to BV and CP.

References

1 Boffa MJ, Wilkinson SM, Beck MH. Screening for corticosteroid contact hypersensitivity. *Contact Dermatitis* 1995; **33**: 149–51.

2 Dooms-Goossens A, Morren M. Results of routine patch testing with corticosteroid series in 2073 patients. *Contact Dermatitis* 1992; **26**: 182–91.

3 Thomson KF, Wilkinson SM, Powell S, Beck MH. The prevalence of corticosteroid allergy in two U.K. centres: prescribing implications. *Br J Dermatol* 1999; **141**: 863–6.

4 Wilkinson SM, Jones MF. Corticosteroid usage and binding to arginine: determinants of corticosteroid hypersensitivity. *Br J Dermatol* 1996; **135**: 225–30.

5 Wilkinson SM, Beck MH. Corticosteroid contact hypersensitivity. what vehicle and concentration? *Contact Dermatitis* 1996; **34**: 305–8.

6 Förström L, Lassus A, Salde L, Niemi K-M. Allergic contact eczema from topical corticosteroids. *Contact Dermatitis* 1982; **8**: 128–33.

7 Reitamo S, Lauerma AI, Stubb S *et al.* Delayed hypersensitivity to topical corticosteroids. *J Am Acad Dermatol* 1986; **14**: 582–9.

8 Coopman S, Degreef H, Dooms-Goossens A. Identification of cross-reaction patterns in allergic contact dermatitis from topical corticosteroids. *Br J Dermatol* 1989; **121**: 27–34.

9 Wilkinson SM. Corticosteroid cross-reactions: an alternative view. *Contact Dermatitis* 2000; **42**: 59–65.

10 Isaksson M, Bruze M, Goossens A, Lepoittevin JP. Patch testing with budesonide in serial dilutions. the significance of dose, occlusion time and reading time. *Contact Dermatitis* 1999; **40**: 24–31.

11 Isaksson M, Gruvberger B, Persson L, Bruze M. Stability of corticosteroid patch test preparations. *Contact Dermatitis* 2000; **42**: 144–8.

12 Lauerma AI, Reitamo S, Förström L. Allergy to topical corticosteroids. In: *Practical Contact Dermatitis* (Guin, JD, ed.). New York: McGraw-Hill, 1995; 575–83.

13 Seukeran DC, Wilkinson SM, Beck MH. Patch testing to detect corticosteroid allergy: is it adequate? *Contact Dermatitis* 1997; **36**: 127–30.