

Patch testing with budesonide in serial dilutions: the significance of dose, occlusion time and reading time*

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Budesonide is advocated as a marker molecule for corticosteroid contact allergy. When patch testing corticosteroids, one must consider their sensitizing potential but also their anti-inflammatory properties, as well as the possibility of different time courses for such properties. The dose-response relationship for budesonide was therefore investigated with regard to dose, occlusion time, and reading time. 10 patients were patch tested with budesonide in ethanol in serial dilutions from 2.0% down to 0.0002% with occlusion times of 48, 24, and 5 h. Readings were on D2, D4, and D7. The 48-h occlusion picked up most positive reactors, 8/10. The D4 reading (48-h occlusion) detected most positive reactors, 8/10, and here 0.002% picked up most contact allergies. Late readings favoured high concentrations. The "edge effect" was noted for several concentrations at early readings. Due to the individual corticosteroid reactivity, the dose-response relationship and the time courses of the elicitation and the anti-inflammatory capacity, several features may be explained, i.e., that lower concentrations may detect budesonide allergy better at early readings, that patients with an "edge reaction" can have positive reactions to lower concentrations.

Key words: corticosteroids; budesonide; dose-response relationship; "edge effect"; patch testing technique; contact sensitivity; serial dilutions; allergic contact dermatitis; false-negative reactions.
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Contact allergy to corticosteroids is no longer a rare phenomenon. Patch test results from Belgium, Finland, Great Britain, and Sweden confirm this, with a contact allergy frequency ranging from 2–5% in consecutive patients being patch tested because of suspected allergic contact dermatitis (1–4). When suspecting corticosteroid contact allergy, specific markers have been advocated, as patch testing with all available corticosteroid molecules is impossible and /or inconvenient in the clinical setting. Above all, tixocortol pivalate (5–7) and budesonide (5, 8, 9) are recommended as markers, and they seem to pick up contact allergies to specific groups of corticosteroids.

When patch testing corticosteroids, one has to take into consideration not only their sensitizing potential but also their anti-inflammatory properties (10), as well as the possibility of different time courses for such properties. The dose-response relationship for corticosteroids may therefore be different from other sensitizers due to an inhibitory action of the corticosteroid itself.

Studies were designed where these considerations were taken into account and with the following 3 major objectives.

(A) To look at the dose-response relationship for budesonide with regard to the following factors: (a) the dose of the corticosteroid tested; (b) the influence of the occlusion time of the sensitizer; (c) the influence of the reading time.

(B) To investigate the potential of budesonide's 2 isomers to evoke allergic patch test reactions in subjects allergic to budesonide.

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Table 1. Results of patch testing with serial dilutions of budesonide in 10 patient hypersensitive to budesonide with the use of different occlusion and reading times; D2, D4, D7=reading on day 2, 4, 7

Pat. no.	Conc. %	Budesonide 5-h occlusion			Budesonide 24-h occlusion			Budesonide 48-h occlusion		
		D2	D4	D7	D2	D4	D7	D2	D4	D7
1	2	—	—	—	—	—	—	++	—	—
	0.2	—	—	—	—	+	—	++	—	—
	0.02	+	+	—	—	+	—	+	—	—
	0.002	+	+	+	+	+	—	+	+	—
	0.0002	+	+	+	—	—	—	+	+	—
2	2	++	++	++	+	++	—	—	++	++
	0.2	++	++	++	+	++	+	—	++	++
	0.02	++	++	+	+	++	+	+	++	+
	0.002	+	++	—	—	++	+	+	++	—
	0.0002	—	++	—	—	—	—	+	+	—
3	2	—	—	—	—	—	—	—	—	—
	0.2	—	—	—	—	—	—	+	—	—
	0.02	—	—	—	—	—	—	+	—	—
	0.002	—	—	—	—	—	—	—	—	—
	0.0002	—	—	—	+	—	—	+	—	—
4	2	—	++	++	—	—	++	—	—	+
	0.2	—	++	++	—	+	—	—	—	+
	0.02	—	—	—	—	+	++	—	+	+
	0.002	—	—	—	—	+	+	—	+	+
	0.0002	+	+	—	—	+	—	—	+	—
5	2	+	—	—	—	++	—	—	+	+
	0.2	—	—	—	—	++	—	—	+	+
	0.02	—	—	—	—	++	—	—	—	+
	0.002	+	+	—	—	—	—	—	++	+
	0.0002	+	+	—	—	++	—	—	+	—
6	2	—	++	+	+	+	+	+	+	++
	0.2	—	++	+	+	+	+	—	+	++
	0.02	—	—	+	—	+	—	—	+	++
	0.002	—	—	—	—	+	—	—	+	+
	0.0002	—	—	—	—	—	—	—	—	—
7	2	—	—	—	—	—	++	—	—	+
	0.2	—	—	—	—	—	—	—	—	—
	0.02	—	—	—	—	—	—	—	—	+
	0.002	+	+	+	—	—	+	—	+	+
	0.0002	—	—	—	—	+	—	—	+	—
8	2	—	—	—	—	—	—	—	—	—
	0.2	—	—	—	—	—	—	—	—	—
	0.02	—	—	—	—	—	—	—	—	—
	0.002	—	—	—	—	—	—	—	—	—
	0.0002	—	—	—	—	—	—	—	—	—
9	2	++	++	++	++	++	++	++	++	+
	0.2	++	++	+	—	++	+	++	++	++
	0.02	++	++	+	+	++	+	+	++	+
	0.002	+	+	—	+	++	+	+	+	—
	0.0002	—	—	—	+	+	—	—	+	—
10	2	—	++	++	—	—	++	—	—	++
	0.2	—	++	++	—	++	++	—	—	++
	0.02	—	++	+	—	+	++	—	+	+
	0.002	—	—	—	+	++	++	—	++	++
	0.0002	—	++	—	+	++	++	+	+++	+

(C) To examine the cross-reactivity pattern between budesonide and its 2 isomers on the one hand and 4 corticosteroid sensitizers, 2 from group B and 2 from group D, on the other hand.

In this article, only study (A) will be dealt with. Studies (B) and (C) will be reported separately.

Materials and Methods

Subjects

10 patients from the Contact Allergy Clinic of the University Hospital, Leuven, Belgium, previously known to be hypersensitive to 1.0% budesonide

tested in ethanol, participated in the study. Informed written consent was given and the study was approved by the Ethics committee of the Katholieke Universiteit Leuven.

Test preparations

All test substances were dissolved in absolute ethanol (99.5% v/v). Budesonide (Astra Draco, Sweden) was dissolved at 2.0% w/v and from this stock solution further dilutions were prepared: 0.2% w/v, 0.02%, 0.002%, and 0.0002%. Since budesonide is a 1:1 mixture of 2 diastereomers, the R and S isomer, and both isomers were also tested in this study at 1.0% as corticosteroids most frequently are, the concentration of budesonide (R+S) being chosen to start at 2.0%.

Patch-test technique

Finn Chambers mounted on Scanpor tape were used. 15 μ l of test solution was applied to the

filter paper disc in the chamber. All patients were tested on the upper back and the different test preparations were placed in a specific order in all patients; the patch test material was removed after 2 days except for 2 columns of patches: the column to the far left was taken off the back after only 5 h, whereas on the far right the patches were removed after 24 h. Reading took place on days 2, 4, and 7. Reactions were evaluated according to ICDRG criteria (11). Additional notes based on morphological signs were also made for each patch test site. This enabled comparisons of morphologies on D2, D4, and D7 in more detail and was used when the "edge effect" (16, 17) was considered.

Results

In Table 1, the patch test results can be seen. Of the 10 patients previously known to be hypersensitive to budesonide, only 9 reacted to budesonide. The dose-response relationship for budesonide with occlusion time 48 h, designated as the number of positive reactors for a specific patch test concentration (Fig. 1a), demonstrated that more patients tested positively to low concentrations of budesonide. The time of occlusion for budesonide was 48, 24, and 5 h for all patch tested concentrations (Fig. 1a-c). When considering the separate patch test concentrations and how many of the total number of tested patients reacted to each one, we found that 48 h occlusion picked up most positive reactors, 8/10 tested. When budesonide was tested with 48-h occlusion in low concentrations and read on D4, the most positive reactors were found, in contrast to high concentrations, where a lower number of positive reactors were found. Occlusion time 24 h picked up 7/10 tested with medium concentrations and read at D4. Occlusion time 5 h detected 5 positive reactors at the most.

When considering each separate patient, all tested concentrations, and the 3 reading times, we found that occlusion for 5 h detected 8/10 tested, and occlusion time 24 and 48 h, respectively, detected 9/10 tested (Table 1).

The times of readings were days 2, 4, and 7 (Table 1). When considering the separate patch test concentrations and how many of the total number of tested patients reacted to each one, we found that early readings (D2) gave a maximum of 5 positive reactors to budesonide (5 h occlusion and patch test concentration 0.002%) (Fig. 1c). D4 readings detected most positive reactors, 8/10, and here low concentrations picked up most contact allergies. Late readings (D7) favoured high concentrations (Fig. 1a).

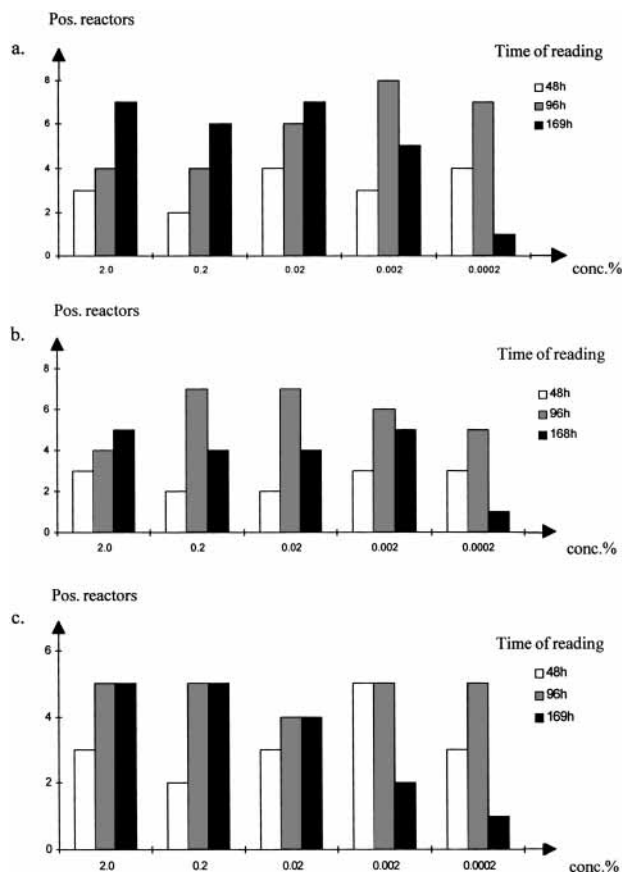


Fig. 1. Number of patients testing positively to various concentrations of budesonide on different reading occasions: (a) with 48-h occlusion time; (b) with 24-h occlusion time; (c) with 5-h occlusion time.

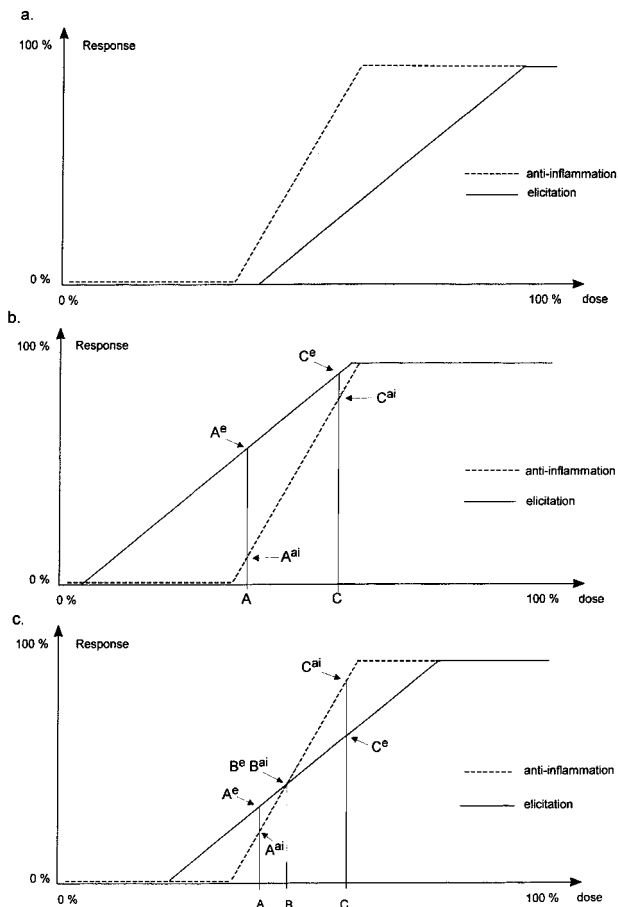


Fig. 2. The interaction between the dose-response relationship for elicitation and anti-inflammatory effect of a corticosteroid in a patient: (a) with low reactivity-weak corticosteroid sensitivity; (b) with high reactivity-strong corticosteroid sensitivity. A^e, C^e =the degrees of elicitation represented by the concentrations A and C, respectively; A^{ai}, C^{ai} =the degrees of anti-inflammation represented by the concentrations A and C, respectively; (c) with an average reactivity-modest corticosteroid sensitivity. A^e, B^e, C^e =the degrees of elicitation represented by the concentrations A, B, and C, respectively; A^{ai}, B^{ai}, C^{ai} =the degrees of anti-inflammation represented by the concentrations A, B, and C, respectively.

When patch testing corticosteroids it is very common to see nonspecific reactions at early readings such as erythema and blanching as well as reactions with a peripheral ring, the so-called "edge effect" (16, 17). These types of reactions were also noted in this study, but they were considered negative and are shown as such in Table 1.

Discussion

Despite corticosteroids having anti-inflammatory properties, sensitization to them still occurs. Currently, patch testing is virtually the only method that can demonstrate that sensitization has taken

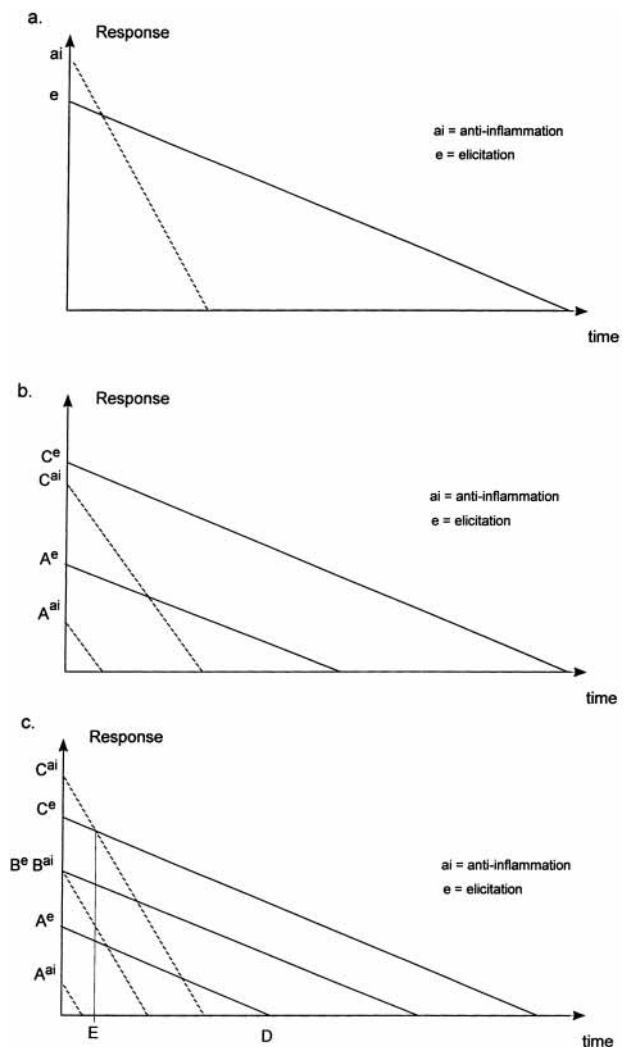


Fig. 3. The significance of the time courses for elicitation and anti-inflammatory effect for positive patch test reactions in patients with corticosteroid hypersensitivity: (a) in a patient with a low corticosteroid reactivity in agreement with Fig. 2a; (b) in a patient with high corticosteroid reactivity and based on 2 different concentrations in agreement with Fig. 2b. A^e, C^e =the degrees of elicitation represented by the concentrations A and C, respectively, in Fig. 2b; A^{ai}, C^{ai} =the degrees of anti-inflammation represented by the concentrations A and C, respectively, in Fig. 2b; (c) in a patient with an average corticosteroid reactivity and based on 3 different concentrations in agreement with Fig. 2c. A^e, B^e, C^e =the degrees of elicitation represented by the concentrations A, B, and C, respectively, in Fig. 2c; A^{ai}, B^{ai}, C^{ai} =the degrees of anti-inflammation represented by the concentrations A, B, and C, respectively, in Fig. 2c; E and D are discussed in the text.

place. When a corticosteroid has sensitized, it is likely that its anti-inflammatory properties will influence its elicitation capacity, i.e., patch test reactions. The dose-response relationship for the anti-inflammatory curve is relatively steep, with a rather narrow range of doses that determine the response between nil and 100%. The time course

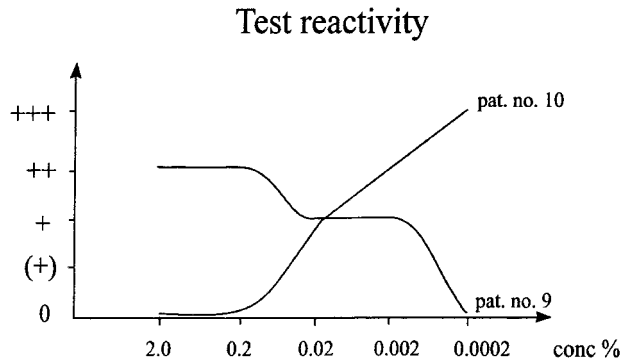


Fig. 4. The dose-response relationship for budesonide in 2 budesonide-hypersensitive patients (patient nos. 9 and 10) patch tested with budesonide in serial dilution with occlusion for 48 h and read on D2 (no. 9) and D4 (no. 10).

of the anti-inflammatory effect is characterized by a rapid onset and disappearance. Considering only the elicitation capacity of a sensitizing corticosteroid, thus disregarding its intrinsic anti-inflammatory effect on the elicitation, there is no reason to believe that the dose-response relationship should be essentially different to non-corticosteroid sensitizers. Taking the dose-response curve and time course of the anti-inflammatory effect of a sensitizing corticosteroid into account, the resulting patch test reactions to this corticosteroid will depend on the individual degree of reactivity to the corticosteroid, the shape of the dose-response curve and the time course of the elicitation. At a given reading time when the anti-inflammatory effect still prevails, 3 main situations may occur.

(I:a) In a situation where there is a low reactivity and elicitation capacity, the anti-inflammatory effect may quench the expression of the elicitation for all corticosteroid concentrations resulting in a negative patch test. This is illustrated in Fig. 2a.

(I:b) The opposite is seen when there is a high reactivity and elicitation capacity. Here, the anti-inflammatory effect will never influence the elicitation in such a way that the patch test reaction will appear negative. This is seen in Fig. 2b.

(I:c) Yet another example is when there is an average reactivity and elicitation capacity. The anti-inflammatory effect of the corticosteroid will quench the patch test reaction with high concentrations tested, while testing with lower concentrations will result in positive reactions. This is illustrated in Fig. 2c.

Besides the situations depicted in Figs. 2a-c, further situations may occur when including the possible significance of the different time courses for the anti-inflammatory effect and the elicitation

capacity in the discussion. As already mentioned, the anti-inflammatory effect will disappear more quickly than the elicitation capacity after the removal of the patch units. Based on the situations in 2a-c, there will be another 3 main situations when the reading time is considered.

(II:a) In a situation where there is such a low reactivity that the patch test reaction is suppressed by the anti-inflammatory effect at early readings (Fig. 2a), the reaction may appear at a later reading, when the anti-inflammatory effect has gone. This can be seen in Fig. 3a.

(II:b) Another situation is depicted in Fig. 3b. Considering Fig. 2b, the patch test reaction will always appear positive, both at early and late readings. Low concentrations give positive patch test reactions that disappear more quickly (A^e, Fig. 3b), compared to higher concentrations (C^e, Fig. 3b) that lead to patch test reactions that prevail longer.

(II:c) Lastly, the situation in Fig. 2c will lead to 3 main different situations depending on where on the dose line (Fig. 2c) you start. When taking into consideration the significance of the time course for the anti-inflammatory and elicitation capacity emerging from point A in Fig. 2c, a situation illustrated as in Fig. 3c will be seen. The test is positive from the start until point D, provided that D represents the threshold of elicitation on that specific reading occasion. Another situation is when you start at point B (Fig. 2c), which represents the intersection of the dose-response curves for the anti-inflammatory and elicitation capacity. At this point, the test is negative. Looking at Fig. 3c and the same concentration and starting when the test is negative, this concentration will yield a positive test immediately after the reading represented by Fig. 2c, since the anti-inflammatory effect has a more rapid disappearance than the eliciting. At a further higher concentration represented by C in Fig. 2c, the test is negative at that particular reading time. Following that particular concentration over time, it will according to Fig. 3c render a positive reaction after the intersection represented by E.

Budesonide at 0.002% with occlusion time 48h and read on D4 was the concentration that picked up most contact allergies, as 8 of the 9 patients that reacted to budesonide reacted to this concentration (Fig. 1). In comparison, only 4 of these 9 reacted to 0.2% (with the same occlusion time and reading occasion), the concentration nearest to the recommended patch test concentration for budesonide, which is 0.1%. The outcome for 0.2% was 6 out of 9 with the same occlusion time (48 h) but read on D7. When patch

testing any sensitizer lacking anti-inflammatory properties in serial dilutions, one would expect the maximal test concentrations to yield the highest number of positive reactors, and that with lowering patch test concentrations, decreasing numbers of positive reactors would be found. Dealing with anti-inflammatory substances and considering the above mentioned hypotheses (Fig. 2a-c, Fig. 3a-c), it was not surprising that we found some patients reacting only to lower concentrations of budesonide instead of to higher (Fig. 2c). When patients represented by Fig. 2c are tested with potent corticosteroids and these are tested with currently recommended high concentrations this can lead to false-negative patch test reactions at early readings.

In this study, only 9 of the 10 patients reacted to budesonide, as 1 of the patients had negative patch test reactions to all tested concentrations. On repeated patch testing there may be great intra-individual variation in test reactivity, as was seen in nickel-sensitive females (12). Presuming that there is also such variation for other sensitizers, including corticosteroids, the reactivity in the patient without demonstrable patch test reactivity could be decreased in this study and in this situation be an example of Fig. 2a. On the standard reading days (D2-D4), 1 patient (no. 9) had a nice reaction series, with strong positive reactions to the highest concentrations and lower reactivity to lower concentrations of the sensitizer and could therefore be representative of Fig. 2b (Fig. 4). In contrast, on D4 patient no. 10 had a totally reverse pattern, with negative reactions to the highest concentrations tested and strongest reaction patterns to the lowest concentrations, like Fig. 2c.

Wilkinson & Beck (13) patch tested 8 patients known to be allergic to budesonide with a dilution series of budesonide in (95%) ethanol (1.0, 0.5, 0.1%) and found no evidence of a dose-related suppression of the patch test reaction at higher concentrations, which led them to suggest that all corticosteroids should be tested at 1.0% in ethanol.

The conclusion that can be drawn from this study is that one and the same concentration cannot be used to detect contact allergy in all budesonide-allergic patients. As with other sensitizers, some patients seem to require the highest concentrations, but unlike other sensitizers, at least those without anti-inflammatory potential, other patients may need a lower concentration. The practical consequence may be that with early readings low concentrations may be preferable, and that with late readings high concentrations may be recommended. There may therefore be an argument

for patch testing with 2 concentrations (high and low).

In patient nos. 2, 6 and 9, high patch test concentrations gave allergic reactions that tended to stay positive longer than the lower concentrations, which is in accordance with patients having a high reactivity and elicitation capacity, schematically drawn in Fig. 2b. On the other hand, when looking at the patients who are representative of average reactivity, as illustrated in Fig. 2c, we have a different situation with lower concentrations testing positively on D4 and tending to disappear quickly, as in patient nos. 1, 4, 5, and 7, while higher concentrations testing negatively on D4 became positive on D7, as in patient nos. 4, 7 and 10.

The occurrence of "ring-shaped" patch test reactions, with features consistent with an allergic morphology, to allergens dissolved in a liquid vehicle has been discussed by Lachapelle et al. and Fyad (14, 15). They also use the term "edge effect" to describe such a patch test reaction. The reaction is more intense at the periphery of the site of application than in the central part. It is thought to be due to accumulation of the chemical at the periphery of the patch test site due to pressure and/or capillary migration. Only exceptionally did they find that this could also be seen with allergens dispersed in petrolatum. However, in the present study, we saw a type of "edge-effect" in which a blank center representing the whole area of the test unit was surrounded by an eczematous infiltrate, in contrast to the ring-shaped reaction described by Lachapelle et al., where the central part is not completely blank and where all the reaction is within the patch test site. Even if in this study the vehicle was a solvent, the "edge effect" is, in contrast to the description of Lachapelle et al., also seen when patch testing with potent corticosteroids like budesonide in petrolatum (16). The explanation of the "edge effect" induced by a corticosteroid is probably different. The corticosteroid "edge effect" seen here is thought to be due to suppression of the allergic reaction under the patch test chamber, because of the intrinsic anti-inflammation from the corticosteroid itself and brought about by a higher concentration of the actual corticosteroid under the patch than just outside it (17, 18). Due to penetration and diffusion factors the concentration of any sensitizer will be highest under the test unit and outside this area one will find gradually decreasing concentrations. Every individual patch test can thus be regarded as a test with a continuous dilution series. Consequently, due to the individual degree of reactivity (elicitation capacity) various situations may occur (Figs. 2a-c). For any given concentration, the

conditions presented in Fig. 2a and 2b mean that there will be no "edge effect". Accordingly, the "edge effect" should only be seen in some patients. When we have the situation illustrated in Fig. 2c one will expect the "edge effect" to appear. Due to occlusion by the patch unit, the corticosteroid concentration will be highest under the patch and the anti-inflammatory effect will quench the patch test reaction under the patch unit, while the corticosteroid concentration outside the patch unit is lower and thus results in a positive reaction. Based on the hypotheses illustrated in Figures 2c and 3c, 3 situations can be predicted when a patient tested with a corticosteroid reacts with an "edge reaction":

- (i) that the concentrations above the concentration yielding an edge will appear negative
- (ii) that lower concentrations than the concentration resulting in an edge will appear positive
- (iii) that the concentration giving the edge or the concentrations above the concentration giving an edge will appear positive at a late reading occasion when the anti-inflammatory effect has vanished.

After 48 h occlusion, the "edge effect" was seen in 6 patients on D2 and/or D4. Considering the same occlusion time, on D2 and/or D4, 5 of the 6 patients had negative reactions to the concentrations above the lowest concentration giving an "edge reaction", and all 6 patients had positive reactions to lower concentrations than the edge concentration. Furthermore, the concentration giving an edge on D2 or D4 led to a positive patch test on D7 in 5 patients. No "edge reaction" could be seen on D7. According to the criteria of the ICDRG, an "edge reaction" can never stand alone as the only proof of contact allergy. On the other hand, this reaction may represent an allergic patch test and should therefore be elucidated further. So as not to miss a contact allergy, a late reading after 1 week should be done or further patch testing with the incriminated corticosteroid at lower concentrations, as these most likely will render positive test readings on D2 or D4. In the light of the difference in individual corticosteroid reactivity, the dose-response relationship, the time-courses of the elicitation and anti-inflammatory capacity, many features that we see when patch testing corticosteroids may be explained, i.e., that lower concentrations may be better to detect contact allergy in some patients, that patients with an "edge reaction" can show negative reactions to higher concentrations than the concentration giving the edge and positive reactions to lower concentrations. Furthermore, that an additional late reading should be performed apart from the tra-

ditional reading times during the period D2 – D4 (4).

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References

1. Doooms-Goossens A, Morren M. Results of routine patch testing with corticosteroid series in 2073 patients. *Contact Dermatitis* 1992; 26: 182–191.
2. Burden AD, Beck MH. Contact hypersensitivity to topical corticosteroids. *Br J Dermatol* 1992; 127: 497–500.
3. Lauerma A I. Screening for corticosteroid contact sensitivity. Comparison of tixocortol pivalate, hydrocortisone-17-butyrate and hydrocortisone. *Contact Dermatitis* 1991; 24: 123–130.
4. Malmkvist-Padoan S, Björkner B, Bruze M, Edman B, Möller H, Svensson Å. *Contact allergy to corticosteroids in Southern Sweden* (abstr). 2nd Congress of the European Society of Contact Dermatitis, 8 October 1994.
5. Lepoittevin J P, Drieghe J, Doooms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. *Arch Dermatol* 1995; 131: 31–37.
6. Doooms-Goossens A et al. (EECDRG). A survey of the results of patch tests with tixocortol pivalate. *Contact Dermatitis* 1989; 20: 158.
7. Wilkinson S M, English J S C. Hydrocortisone sensitivity: a prospective study of the value of tixocortol pivalate and hydrocortisone acetate as patch-test markers. *Contact Dermatitis* 1991; 25: 132–133.
8. Gonzalo Garijo M A, Bobadilla Gonzáles P. Cutaneous-mucosal allergic contact reaction due to topical corticosteroids. *Allergy* 1995; 50: 833–836.
9. Degreef H, Doooms-Goossens A. The new corticosteroids: are they effective and safe? *Dermatol Ther Clin* 1993; 11: 155–160.
10. Doooms-Goossens A, Verschaeye H, Degreef H, Van Berendoncks J. Contact allergy to hydrocortisone and tixocortol pivalate: problems in the detection of corticosteroid sensitivity. *Contact Dermatitis* 1986; 14: 94–102.
11. Fregert S. *Manual of contact dermatitis*, 2nd edition. Copenhagen: Munksgard, 1981.
12. Hindsén M, Bruze M, Christensen O B. Individual variation in nickel patch test reactivity. *American Journal of Contact Dermatitis*, in press.
13. Wilkinson S M, Beck M H. Corticosteroid contact hypersensitivity: what vehicle and concentration? *Contact Dermatitis* 1996; 34: 305–308.
14. Lachapelle J M, Tennstedt D, Fyad A, Masmoudi M L, Nouaigui H. Ring-shaped positive allergic patch test reactions to allergens in liquid vehicles. *Contact Dermatitis* 1988; 18: 234–236.
15. Fyad A, Masmoudi M L, Lachapelle J M. The "edge-effect" with patch test materials. *Contact Dermatitis* 1987; 16: 147–151.
16. Doooms-Goossens A, Pauwels M, Bourda A, Degreef H, Kinget R. Patch testing with corticosteroids in xerogel formulations. *Contact Dermatitis* 1992; 26: 206.

17. Dooms-Goossens A, Degreef H. Clinical aspects of contact allergy to corticosteroids. *Dermatology* 1994; 189(Suppl 2): 54–55.
18. Dooms-Goossens A. Contact dermatitis to topical corticosteroids: diagnostic problems. In: Menné T, Maibach H I (eds): *Exogenous dermatoses: environmental dermatitis*. Boca Raton: CRC Press, 1991: 299–310.

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