

Patch testing with corticosteroid mixes in Europe

A Multicentre Study of the EECDRG

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This study investigated whether a corticosteroid mix containing tixocortol pivalate, budesonide, and hydrocortisone-17-butyrate could detect contact allergy to corticosteroids. 2 corticosteroid mixes, 1 with a high (mix I) and 1 with a low (mix II) concentration and the 3 individual constituents, each at 2 concentrations, were inserted into the standard series of 16 participating clinics. Tests were read on day (D) 3 or 4. 5432 patients were tested, and 110 (2.0%) had positive reactions to at least 1 of the 8 test preparations. Of the 8 preparations, mix I identified most allergic patients, followed by mix II, budesonide 0.10%, budesonide 0.002%, and tixocortol pivalate, both concentrations (1.0 and 0.10%) tracing the same number. With the mixes, 53.2–59.6% of tixocortol pivalate allergy was missed. 47 patients were allergic to either concentration of tixocortol pivalate, 25% of these only to 1.0% and another 25% only to 0.10%. Testing with mix I and tixocortol pivalate 0.10% picked up 98/110, testing with tixocortol pivalate 1.0% and 0.10% and budesonide 0.10% picked up 105/110. 3379 patients were read on both D3 or D4 as well as on D7. Without a late reading (D7), up to 30% of contact allergy to corticosteroid markers was missed.

Key words: contact allergy; corticosteroids; mixes; tixocortol pivalate; budesonide; hydrocortisone-17-butyrate; medicaments; patch testing technique. © Munksgaard, 2000.

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Contact allergy to topical corticosteroids is common enough, with frequencies ranging from 2.9%–5.8% (1–4), to justify patch testing with corticosteroids in standard series. Both the frequency of contact allergy to these substances and the causal corticosteroids vary from one centre to another (5). The reasons for this are thought to be the type of corticosteroids available on the market, the

‘treatment tradition’ (5), the test substance, vehicles, concentrations, and methods used to detect corticosteroid sensitivity. 3 substances most frequently used and recommended as screening markers for the detection of contact allergy to corticosteroids are tixocortol pivalate for class A (2), budesonide for class B (6), and hydrocortisone-17-butyrate (Hc-17-B) for class D corticosteroids (2). They are usually patch tested at 1.0, 0.10, and 1.0% in ethanol, respectively, and for

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budesonide and tixocortol pivalate petrolatum is also used.

Patch testing with a mix would save both space and time (7). To assess the reliability of a mix in detecting contact allergy to its constituents, patch testing has to be carried out simultaneously in consecutive dermatitis patients with the mix and its constituents, in the same vehicle and at the same concentrations as used in the mix. A corticosteroid mix ought to contain the 3 marker molecules tixocortol pivalate, budesonide, and Hc-17-B. The aim of this study was to investigate whether a corticosteroid mix could be used to detect contact allergy to corticosteroids. Due to insufficient knowledge of the interaction between the eliciting and anti-inflammatory effects in one and the same sensitizer, as well as the anti-inflammatory effect of one corticosteroid exerted on the possible allergic contact reaction to the other corticosteroids in the mix, we used 1 mix with high concentrations and 1 mix with lower concentrations of the respective corticosteroids. As a corticosteroid mix might be useful in a standard series, we used petrolatum instead of ethanol for vehicle.

Materials and Methods

The study was divided into 2 parts.

Part I

3 centres within the European Experimental Contact Dermatitis Research Group (EECDRG) participated from February 1997 until November 1997. 1109 dermatitis patients (406 men, 703 women) were patch tested.

Part II

An additional 13 centres within the EECDRG, besides the 3 centres already mentioned, participated from November 1997 until 30 June 1998. 4323 (1553 men, 2770 women) were patch tested.

Test substances

2 corticosteroid mixes, 1 with a high (mix I) and 1 with a low (mix II) concentration, and the 3 individual constituents, each at 2 concentrations, totalling 8 patches, were inserted into the standard series of each centre. The concentrations of the 3 separate corticosteroids when tested separately and in the mixes, the vehicles, the suppliers and the batch numbers (when applicable) are given in Table 1. The test preparations were prepared at the Department of Occupational and Environmental

Dermatology in Malmö, Sweden, and delivered to all participating test laboratories.

Patch testing

Consecutive dermatitis patients were patch tested with all 8 patches. Patches were to remain on the back for 2 days and mandatory readings had to be carried out on day (D) 3 or 4 and if possible, consistently, but voluntarily, on D7. Readings were according to the guidelines of ICDRG (8). 9 clinics had D3 or D4 and D7 as their mandatory reading days, but apart from these clinics, there was a great variation in reading times other than the mandatory D3 or D4.

In part I, 584 patients were patch tested with the Finn Chamber system and 525 with the Van der Bend system. In part II, 3600 were patch tested with Finn Chambers and 723 with Van der Bend chambers. Each centre used the patch test system they had at that time.

Studies A to E

5 different topics were studied (A to E), each described separately to facilitate clarification.

Study A

The outcome of patch testing with mix I (high concentration) versus its corticosteroid constituents was compared. Also, the number of patients reacting positively to mix I and simultaneously to the separate markers, as well as the number of patients that did not react to mix I but to the separate markers, were looked at.

Study B

The same comparisons were made for mix II (low concentration) and its corticosteroid constituents as in study A.

Study C

A comparison was made of the yield of positive reactions between mix I, mix II, and their individual components in the total number of patch tested individuals. Furthermore, the individuals reacting simultaneously to the 2 concentrations of the respective sensitizer were looked at.

Study D

The outcome of a patch test made up of 2 test preparations, tested separately but simultaneously, was compared in all 28 possible combinations to

Table 1. Concentration, batch and supplier of all test substances (in petrolatum) in part I and part II of the study

	Conc. % w/w	Part I Batch 1	Part II	
			Batch 1	Batch 2
mix I	1.0+0.1+1.0	A+B	^{a)} A+B	
tixocortol pivalate	1.0	B		B
budesonide	0.1	A	A	
Hc-17-B	1.0	A	B	
mix II	0.1+0.002+0.1	A+B	^{a)} A+B	
tixocortol pivalate	0.1	B		B
budesonide	0.002	A	A	
Hc-17-B	0.1	A	B	

A=Yamanouchi Pharma, Denmark, B=Chemotechnique, Sweden. All test preparations were prepared at the Department of Occupational and Environmental Dermatology, Malmö, Sweden.

^{a)} Tixocortol pivalate batch 2.

find the combination that detected most allergic individuals. Excluding the 2 mixes, the same comparison was made for a patch test made up of 3 test preparations in all 20 possible combinations, to find the combination that detected most allergic individuals.

Study E

The outcome of 1 patch test reading on D3 or D4 was compared to 2 readings on D3 or D4 and D7 for the 8 test preparations in the 9 centres that had both D3 or D4 and D7 as mandatory reading occasions. 3379 dermatitis patients were tested with 2 readings in this way, 269 with the Van der Bend technique and the rest with the Finn Chamber technique.

Statistics

Fisher's exact test, logistic regression analysis with standard errors corrected for clustering on patient identity, and the exact binomial test were used.

Results

No cases of patch test sensitization to any of the tested corticosteroids were recorded.

Part I

24/1109 (2.2%) dermatitis patients were found to react to at least 1 of the 8 corticosteroid test preparations on D3 or D4.

Part II

86/4323 (2.0%) patients were found to be allergic to at least 1 of the 8 preparations on D3 or D4.

Parts I and II

The 3 departments that participated in both part I and II had 997 patients that were tested in part II and 25/997 (2.5%) were found to be allergic to at least 1 of 8 test preparations. When comparing the contact allergy rates to the respective test prep-

Table 2. Studies A and B: the number of patients with positive reactions to mix I and mix II and their corticosteroid components, and the reactions to these components seen in the mix I/II-positive and mix I/II-negative patients; the total no. of patients reacting to mix I/II and/or any of the 3 incorporated corticosteroids was 98/91, respectively

	Concentration (% w/w)	No. patients reacting	% of total no.	Positive reactions to a separate corticosteroid in patients with and without mix I/II reactions				
				Mix-positive patients		% of total no.	Mix-negative patients	
				mix I	mix II		mix I	mix II
mix I	2.1	66	67.3					
t.p.	1.0	47	48.0	22		22.4	25	
bud.	0.1	54	55.1	49		50.0	5	
Hc-17-B	1.0	28	28.6	24		24.5	4	
mix II	0.202	59	64.8					
t.p.	0.1	47	51.6		19	20.9		28
bud.	0.002	48	52.7		45	49.5		3
Hc-17-B	0.1	26	28.6		24	26.4		2

arations on D3 or D4 in the 3 centres that had participated in part I and II, no statistically significant differences were found between part I and II (Fisher's exact test, $p > 0.24$). Hence, figures were summarized from part I and II, and in the following text the results are based on that sum and only on reading time D3 or D4 if not stated otherwise. In this way, 5432 patients were tested with the 8 test preparations and 110 were found to be positive to at least 1 of the 8 preparations, which gave a contact allergy frequency of 2.0%.

In Table 2, the patch test results show that, of the 98 individuals who reacted to mix I and/or any of the 3 incorporated corticosteroids, mix I traced most, followed by budesonide, 66 and 54, respectively. 49 of the 98 individuals had contact allergies to budesonide and mix I simultaneously, as compared to 22 for tixocortol pivalate and mix I. Of the 71 individuals with a positive reaction to budesonide 0.10% and/or mix I, 17 reacted exclusively to the mix while only 5 were mix I negative ($p = 0.017$). Hence, 49/71 reacted to both mix I and budesonide

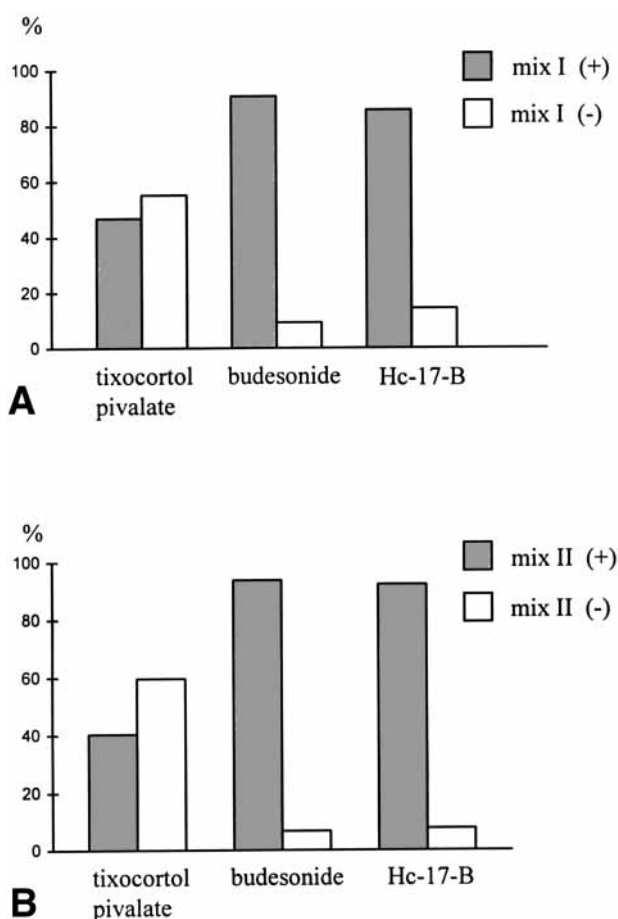


Fig. 1. Studies A and B. The % of tixocortol pivalate-, budesonide-, and Hc-17-B-positive patients (47, 54, and 28, and 47, 48, and 26, respectively) picked up by patch testing with mix I/II (+) and missed by patch testing with mix I/II (-).

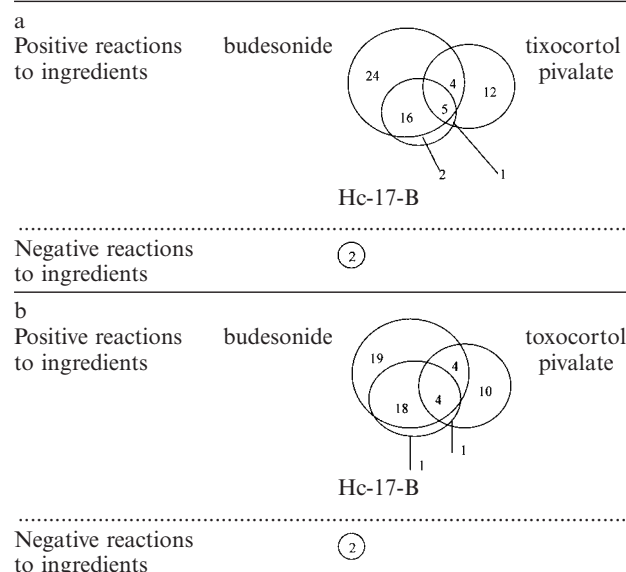


Fig. 2. Studies A and B. The 66 mix I-positive (a) and 59 mix II-positive (b) patients and their simultaneous positive and negative reactions to the corticosteroids in mix I (a) and II (b), respectively.

0.1%. Comparison of the mix I reaction rates for individuals reacting to either tixocortol pivalate (13/37, 35%) or budesonide (40/44, 91%), disregarding those with a positive reaction to both components, showed a statistically significant difference ($p < 0.001$, Fisher's exact test). Similarly there was a significant difference ($p = 0.001$) with respect to mix I reactions between tixocortol pivalate (16/40, 40%) and Hc-17-B (18/21, 86%). Only 6 individuals were simultaneously positive to Hc-17-B and negative to budesonide, which makes it hard to be conclusive concerning any differences found.

In contrast, 25 of the 98 (25.5%) were allergic to tixocortol pivalate but not to mix I, while the corresponding %s for budesonide and Hc-17-B were 5.1% and 4.4%, respectively.

Fig. 1 shows that only 46.8% of the tixocortol pivalate-allergic patients were traced with mix I and, consequently, 53.2% were missed. 90.7% of the budesonide-allergic and 85.7% of the Hc-17-B-allergic patients were traced with mix I.

Fig. 2 shows how the 66 mix I-positive patients reacted to the 3 corticosteroid constituents when patch tested simultaneously with these.

Study B

In Table 2 it is shown that, of the 91 individuals, mix II traced most, followed by budesonide. 45 of the 91 individuals were allergic to budesonide and mix II simultaneously, as compared to 19 for tixocortol pivalate and mix II. Comparison of the

Table 3. Study C: the number of patients with positive patch test reactions to the 2 concentrations of the same type of test preparation (mix, budesonide, tixocortol pivalate, Hc-17-B) in 5432 patch tested dermatitis patients

	And/or	%	Concentrations					
			Only high	%	Only Low	%	Both	%
mix	69	100	10	14.5	3	4.3	56	81.2
budesonide	60	100	12	20.0	6	10.0	42	70.0
tixocortol pivalate	63	100	16	25.4	16	25.4	31	49.2
Hc-17-B	32	100	6	18.8	4	12.5	22	68.7

mix II reaction rates for individuals reacting to either tixocortol pivalate (11/39, 28%) or budesonide (37/40, 93%), disregarding those with a positive reaction to both components, showed a statistically significant difference ($p < 0.001$, Fisher's exact test). Similarly there was a significant difference ($p < 0.001$) with respect to mix II reactions between tixocortol pivalate (14/41, 34%) and Hc-17-B (19/20, 95%). Only 4 individuals were simultaneously positive to Hc-17-B and negative to budesonide, which makes it hard to be conclusive concerning any differences found.

In contrast, 28 of the 91 (30.8%) were allergic to tixocortol pivalate but not to mix II.

Fig. 1 shows how 59.6% of tixocortol pivalate allergy was missed when patch testing with mix II. 93.8% of budesonide allergy and 92.3% of Hc-17-B-allergy was traced with mix II.

Fig. 2 shows how the 59 mix II-positive patients reacted to the 3 corticosteroid constituents when patch tested simultaneously with these.

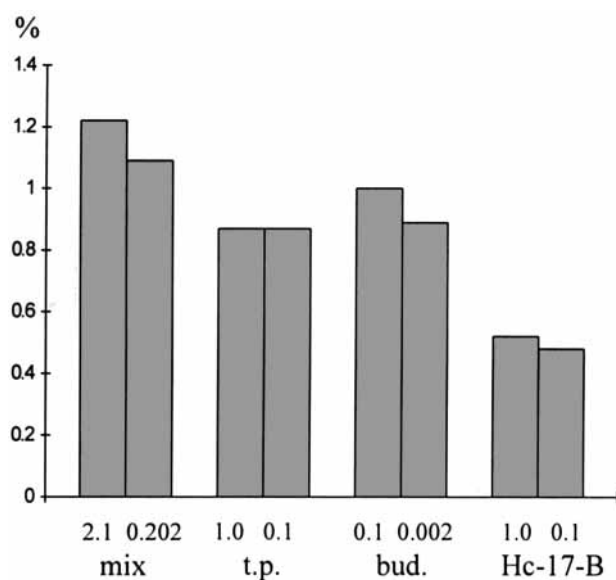


Fig. 3. Study C. The frequency of contact allergy to mix I, II, and their corticosteroid components in 5432 patch tested dermatitis patients.

Study C

Table 3 depicts that a majority of the patients who reacted to the mixes and the separate corticosteroids reacted to both concentrations simultaneously. The 2 concentrations of tixocortol pivalate detected the same number of patients but, for all other test preparations, the high concentrations traced numerically more. The differences were however not statistically significant (based on exact binomial test of equal proportions for low and high concentrations among individuals reacting exclusively to one concentration only). For some patients contact allergy was traced only by using the low concentrations, 1 example being tixocortol pivalate, where 25.4% of the tixocortol pivalate-allergic patients were traced only by testing with 0.10%. In Fig. 3, a bar chart shows the frequency

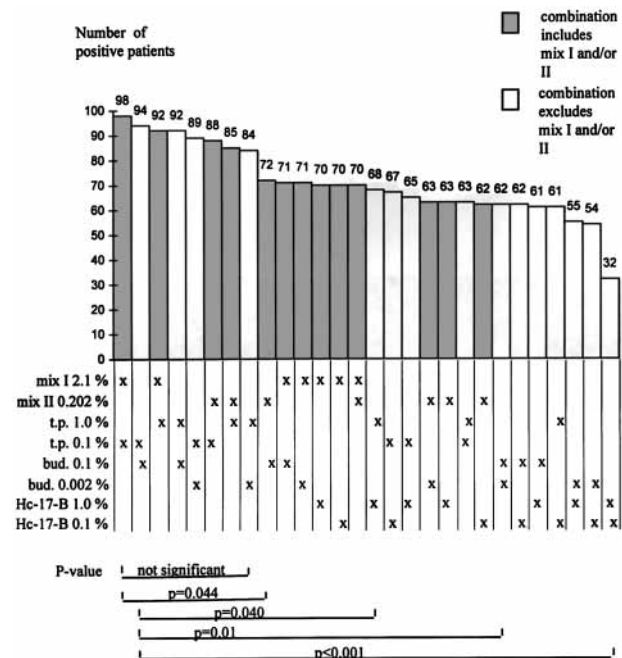


Fig. 4. Study D. The number of positive patients when patch testing with combinations of 2 test preparations. The test preparations included in a combination are marked with an x. P-values are given.

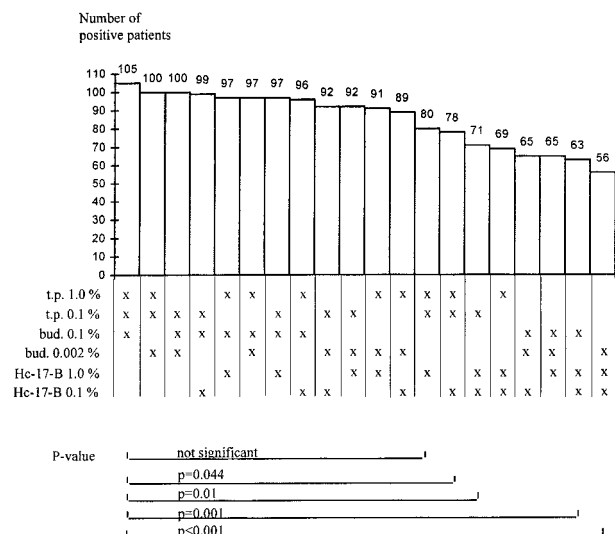


Fig. 5. Study D. The number of positive patients when patch testing with combinations of 3 test preparations. The test preparations included in a combination are marked with an x. P-values for the comparisons are given.

of positive reactions for the different test preparations.

Study D

Fig. 4 shows the number of corticosteroid-allergic patients found when patch testing with 2 test preparations simultaneously. Mix I and tixocortol pivalate 0.10% detected most. The highest yield when the combination did not include a mix was 94, namely with tixocortol pivalate 0.10% and budesonide 0.10%. A significant difference exists between 98 and 72 ($p=0.044$, binomial test without correction), and also between 94 and 68 ($p=0.040$). Fig. 5 alternatively shows the results with 3 test preparations excluding the 2 mixes. Both concen-

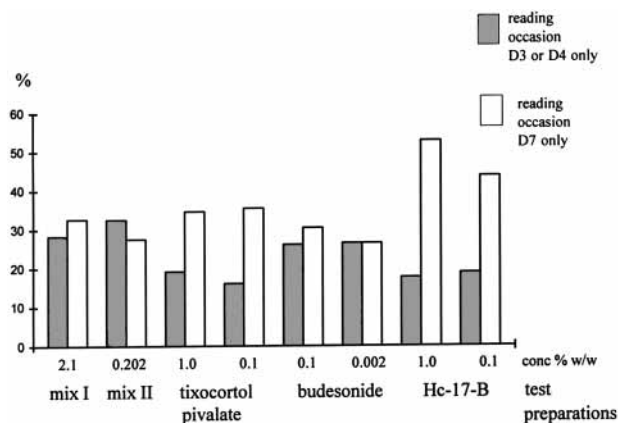


Fig. 6. Study E. The % of missed positive patients when comparing reading days D3 or D4 to D7.

trations of tixocortol pivalate and budesonide 0.10% detected most, 105 patients. A significant difference is found between 105 and 78 ($p=0.044$, binomial test without correction).

Study E

Table 4 shows the outcome of 1 versus 2 reading times and the % of missed positive patch test reactions when reading was done only on D3 or D4 on the one hand, or on D7 on the other. The number of missed reactions for D3 or D4 only varied for the different test preparations between 16 to 33%, with the 95% confidence interval proportionately wide due to few observations (Table 4). For the whole material, 24% was missed. Fig. 6 illustrates this. For the respective test preparations and the high and low concentrations, the figures were very similar when looking at the separate reading times, and for D3 or D4 only, no significant differences were found either between the test preparations or

Table 4. Study E. The yield of positive patients when comparing reading day D3/D4 to the 2 reading days D3/D4 and D7 in all 3379 patients that were read on both D3/D4 and D7; the 95% confidence intervals are given for the respective reading days

Test preparation	Concentration in % w/w	Positive reactions				% missed if reading			
		D3 or D4 and/or D7	only		both D3 or D4 and D7	only		only	
			D3 or D4	D7		D3 or D4	95% confidence interval	D7	95% confidence interval
mix I	2.1	46	15	13	18	28.3	(16–43)	32.6	(20–48)
mix II	0.202	40	11	13	16	32.5	(19–49)	27.5	(15–44)
tixocortol pivalate	1.0	26	9	5	12	19.2	(7–39)	34.6	(17–56)
tixocortol pivalate	0.1	31	11	5	15	16.1	(5–34)	35.5	(19–55)
budesonide	0.1	46	14	12	20	26.1	(14–41)	30.4	(18–46)
budesonide	0.002	34	9	9	16	26.5	(13–44)	26.5	(13–44)
Hc-17-B	1.0	17	9	3	5	17.6	(4–43)	52.9	(28–77)
Hc-17-B	0.1	16	7	3	6	18.8	(4–46)	43.8	(20–70)
total		256	85	63	108	24.6		33.2	

the concentrations in this material ($p=0.49$, logistic regression analysis). For D7 only, again no significant difference was found between the concentrations, but the proportion missed differed significantly between the preparations ($p=0.02$). This finding was primarily due to differences between Hc-17-B on the one hand and budesonide and the mixes on the other.

Discussion

The aim was to see if a mix could trace contact allergy to corticosteroids, whereas the assessment of clinical relevance was not an option.

It is common knowledge that especially potent corticosteroids, when patch tested, can give blanching and erythema at the patch test site at early readings as a result of a physiological phenomenon. These effects can usually be discriminated from contact allergy to corticosteroids. In this investigation, some centres had made notes on these effects consistently while others had not, so they are not reported in figures anywhere. Patch testing with a corticosteroid mix has been performed in a study from Portugal and Belgium (9). 1.8% of their tested patients were positive to the mix. When tested separately later, budesonide was the most frequent positive allergen (0.6%), followed by tixocortol pivalate (0.38%) and Hc-17-B (0.37%). Only 7/57 (12.3%) patients that were positive to the mix did not react to the individual components. General conclusions from this study are, however, hard to draw, as simultaneous patch testing with the separate constituents was not done. This study is an example of the necessity to patch test simultaneously with a mix and its constituents, since the mix I-negative but tixocortol pivalate-positive patients would have been missed, had not this parallel testing been undertaken. The choice of patch test concentrations for the 3 corticosteroids in the mix was not obvious, which is why we chose 2 mixes. In a recent article (10), the interplay between the dose-response relationship for elicitation and anti-inflammation of a sensitizing corticosteroid was discussed considering early readings (D2-D4). It was hypothesized that in an individual with high patch test reactivity to a sensitizing corticosteroid, elicitation leading to a positive patch test reaction was never inhibited by the anti-inflammatory effect of that corticosteroid. Thus, in such an individual, high patch test concentrations, such as are recommended worldwide, as well as low, can still be used. On the other hand, an individual with medium reactivity to a sensitizing corticosteroid was shown to need low patch test doses to achieve a positive patch test reaction. Higher doses led to false-negative patch test reac-

tions due to anti-inflammation dominating elicitation at that point. An individual with medium reactivity thus needs low patch test concentrations when tested. When patch testing consecutive dermatitis patients in a screening fashion, we lack the knowledge as to how many individuals represent the group with high reactivity or the group with medium reactivity. Therefore it seemed necessary to use both the currently recommended high doses and low doses of these marker molecules in the mix testing. Commercial corticosteroid preparations are used in the same therapeutic range as the high patch test concentrations used all over the world. Regarding low doses, we had already seen that budesonide patch tested at 0.002% in ethanol picked up most positive reactors when 10 patients, known from previous patch testing to be allergic to budesonide, were patch tested in serial dilutions from 2.0% down to 0.0002% (10). We had also seen that 1.0% and 0.10% Hc-17-B in ethanol picked up contact allergy equally well in these individuals. A pilot study showed 4 patients, previously known to be allergic to tixocortol pivalate, to react simultaneously to 1.0% and 0.10% tixocortol pivalate. Another major reason to use low concentrations of corticosteroids in a mix concerns the fact that the lower concentration of an individual constituent that can be used to trace contact allergy to it, the less suppression this constituent ought to exercise on the development of allergic patch test reactions to the other constituents. Concerning the choice of patch test vehicle, several studies have shown that the patch test results for budesonide and tixocortol pivalate dispersed in petrolatum or ethanol are equivalent (3, 5).

Study A

Mix I picked up most of the corticosteroid-allergic patients (Table 2) and therefore seems to be superior if only 1 patch test preparation is used, but as the mix missed 53.2% of tixocortol pivalate allergy (Fig. 1), it cannot be recommended with the present composition. Of the separate corticosteroids tested, budesonide 0.10% was superior in detecting corticosteroid allergy, with 55.1% reacting (Table 2). As Hc-17-B was tested in petrolatum, even though ethanol is recommended, there might have been false-negative reactions. A study comparing Hc-17-B in petrolatum and ethanol tested simultaneously in 3326 consecutive dermatitis patients revealed the ethanol preparation to be the most sensitive of the 2, not however substantiated by any figures or statistical calculations in the article (11). In the mix, budesonide and Hc-17-B seem to inhibit the development of the positive patch test reaction to tixocortol pivalate, and

therefore a corticosteroid mix containing budesonide and Hc-17-B should not contain tixocortol pivalate.

Study B

Virtually the same results were seen and the same discussion could be applied here as in study A.

Study C

Even if the numerical value for mix I was higher than that of mix II, no statistically significant difference between the values was found. A higher positive outcome for mix II could have been expected as a low concentration of an individual constituent could be expected to be less inhibiting of the development of positive patch test reactions to the other constituents. This was the case for budesonide and Hc-17-B, when looking at the mix II-positive patients and how they had reacted to the separate sensitizers, as the % of budesonide- and Hc-17-B-positive patients picked up by patch testing with mix II exceeded that of mix I (Fig. 1). 2 of the mix I-positive and 2 of the mix II-positive patients (4 different individuals) had no reactions at all to the 3 respective markers (Fig. 2). The reason for this is not clear. A late (D7) reading did not alter this (data not shown).

A comparison between the 2 concentrations of budesonide or both concentrations of Hc-17-B revealed no statistically significant difference, even if the numerical values were higher for the high concentrations of both sensitizers (Table 3). A majority of the allergic patients reacted simultaneously to both concentrations of the respective sensitizer (Table 3), even budesonide, which is extraordinary, considering its 50-fold concentration difference. As we lack the knowledge of what reactivity consecutive patients have to different sensitizers, we cannot know the optimal concentration for each patient. As more individuals reacted to the high budesonide and Hc-17-B concentration, it seems likely that a majority belonged to the group with high patch test reactivity. Mix I and II detected most allergic patients followed by budesonide 0.10%. Concerning the concentration of the 2 budesonide preparations, the gap from 0.10% to 0.002% is wide and merits further investigation, in which a dilution series of budesonide in petrolatum with narrower concentration gaps should be used. Such an investigation is already being undertaken within the EECDRG.

Furthermore, both high and low concentrations of tixocortol pivalate detected the same number of individuals. Generally, to minimize the risk of patch test sensitization, the concentrations used

should be as low as possible, and this probably also applies to corticosteroids. Tixocortol pivalate is rather expensive and, summarizing these factors, patch testing with tixocortol pivalate 0.10% can be recommended.

Study D

Mix I plus tixocortol pivalate 0.10% detected most allergic patients (98). As discussed earlier, a mix with the present composition as in this study is not an option. On the other hand, if only 2 test preparations with individual corticosteroids can be used, tixocortol pivalate 0.10% plus budesonide 0.10% were shown to be superior and could thus be recommended. It is noteworthy that it was the low concentration of tixocortol pivalate that was present in this combination. Again, when considering 3 test substances, interestingly but expectedly both tixocortol pivalate concentrations and budesonide 0.10% were present in the combination that detected most allergic patients (105).

Study E

Reading corticosteroid patch tests on 2 different occasions (D3 or D4 and D7) increased the number of patients that were found to be allergic to these corticosteroids. The % of missed reactions when reading only on D3 or D4 was virtually the same for both tested concentrations of the respective sensitizer. Figures ranged from 16.1% to 32.5%. It was surprising that budesonide also showed similar figures, even though the concentration gap was 50-fold. These figures are unacceptable and corticosteroid testing cannot therefore be recommended without a late reading after a week in addition to a D3 or D4 reading. A therapeutic agent/sensitizer testing negatively on D2-D4 will be considered by most dermatologists as permission to continue to use, or start to use, this agent topically. For a patient with a dermatitis with a multifactorial background, e.g., most hand eczemas, the allergic contact contribution may not be the most important factor but may be the only factor that can permanently be changed and thus alter the spread and severity of the dermatitis. In this situation, when a sensitizer has tested negatively and read only on D3 or D4 and then is given to a hypersensitive patient, it is easy to overlook the significance of the exposure to this sensitizer for the chronicity of the dermatitis (12).

When read only on D7, both Hc-17-B preparations were on top concerning the % of missed allergy. Furthermore, when looking at the positive reactions present on D3 or D4 and remaining positive on D7 for the respective test preparation of

the individual corticosteroids, both concentrations of Hc-17-B had the lowest %, with 35.7% (5 of 14) and 46.2% (6 of 13) for 1.0% and 0.10%, respectively, while the corresponding figures for tixocortol pivalate and budesonide were in the range 57.1–64.0% (12 of 21 for tixocortol pivalate 1.0% and 16 of 25 for budesonide 0.002%). The differences were however not statistically significant. Still, one possible explanation for the quick disappearance of the Hc-17-B reactions may be metabolism in the skin.

As already mentioned, patch testing with mix I or mix II missed 53.2% and 59.6% of tixocortol pivalate allergy, respectively, using only a D3 or D4 reading. Even with an additional late reading (D7) these figures did not significantly decrease (data not shown). Furthermore, apart from missing up to 30% of corticosteroid allergy if a late reading is not done, positive patch test reactions can also manifest themselves even after 7 days without having to be a sign of patch test sensitization, making the question as to whether sensitization has taken place hard to solve (13, 14).

To summarize, if only 1 test preparation can be used, patch testing with a corticosteroid mix such as ours is an option. However, as a substantial number of tixocortol pivalate-positive patients will be missed, testing with a mix cannot be recommended with the present ingredients. Among the separate test substances, budesonide was the best one to pick up contact allergy to corticosteroids, followed by tixocortol pivalate, for which the low concentration 0.10% can be recommended. The significance of a late patch test reading on D7 was substantiated, as 30.0% of contact allergy to corticosteroid markers was missed with a single D3 or D4 reading.

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References

1. Burden A D, Beck M H. Contact hypersensitivity to topical corticosteroids. *Br J Derm* 1992; 127: 497–500.
2. Lauerma A I. Screening for corticosteroid contact sensitivity. Comparison of tixocortol pivalate, hydrocortisone-17-butyrate and hydrocortisone. *Contact Dermatitis* 1991; 24: 123–130.
3. Doms-Goossens A, Morren M. Results of routine patch testing with corticosteroid series in 2073 patients. *Contact Dermatitis* 1992; 26: 182–191.
4. Wilkinson S M, Cartwright P H, English J S C. Hydrocortisone: an important cutaneous allergen. *Lancet* 1991; 337: 761–762.
5. Doms-Goossens A, Meinardi M M H M, Bos J D, De-greaf H. Contact allergy to corticosteroids: the results of a two-centre study. *Br J Derm* 1994; 130: 42–47.
6. Lepoittevin J P, Drieghe J, Doms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. *Arch Dermatol* 1995; 131: 31–37.
7. Mitchell J C. Patch testing with mixes. Note on mercapto-benzothiazole mix. *Contact Dermatitis* 1981; 7: 98–104.
8. Fregert S. *Manual of contact dermatitis*, 2nd edition. Copenhagen: Munksgaard, 1981.
9. Pecegueiro M. Contact allergy to topical corticosteroids: a screening study with a corticosteroid mix. *Contact Dermatitis* 1995; 33: 196–197.
10. Isaksson M, Bruze M, Goossens A, Lepoittevin J-P. Patch testing with budesonide in serial dilutions: the significance of dose, occlusion time and reading time. *Contact Dermatitis* 1999; 1: 24–31.
11. Reitamo S, Lauerma A I, Förström L. Detection of contact hypersensitivity to topical corticosteroids with hydrocortisone-17-butyrate. *Contact Dermatitis* 1989; 21: 159–165.
12. Bruze M, Edman B, Malmkvist-Padoan S, Svensson Å, Björkner B, Möller H. *The significance of a second patch test reading after one week*. In manuscript form.
13. Le Coz C J, El Bakali A, Untereiner F, Grosshans E. Active sensitization to budesonide and para-phenylenediamine from patch testing. *Contact Dermatitis* 1997; 39: 153–155.
14. Isaksson M, Bruze M, Björkner B, Hindsén M, Svensson L. The benefit of patch testing with a corticosteroid at a low concentration. *Am J Contact Dermatitis* 1999; 10: 31–33.

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