Acta Dermatovenerol Croat 2008;16(2):72-78 CLINICAL ARTICLE

Contact Allergy to Glucocorticosteroids in Patients with Chronic Venous Leg Ulcers, Atopic Dermatitis and Contact Allergy

Maria Zmudzinska, Magdalena Czarnecka-Operacz, Wojciech Silny

Department of Dermatology, Allergic Diseases Diagnostic Centre, Poznan University of Medical Sciences, Poznan, Poland

Corresponding author:
Maria Zmudzinska, MD
Department of Dermatology,
University of Medical Sciences,
ul. Przybyszewskiego 49,
60-355 Poznan,
Poland
m.zmudzinska@wp.pl

Received: January 3, 2008
Accepted: April 30, 2008

SUMMARY The aim of the study was to assess the prevalence of contact allergy to glucocorticosteroids in patients with chronic venous leg ulcers (CVLU), atopic dermatitis (AD) and contact dermatitis (CD), and in a group of healthy individuals; and to estimate differences among these patient groups. Patch tests with the European standard series, antibiotics, glucocorticosteroid contact allergy screening markers and ointment vehicles were performed in a population of 140 patients. Positive patch tests results were recorded in 80% and contact allergy to glucocorticosteroids in 40% of CVLU patients. In the group of AD patients, the respective figures were 30% and 3%. In the group of CD patients, allergic type of disease was detected in 80% and positive patch tests for glucocorticosteroids in 20% of patients. In healthy individuals, allergic contact reaction was observed in 17% of cases. Statistically significant differences among patient groups were found according to the prevalence of contact allergy, polyvalent allergy and contact allergy to glucocorticosteroids. We suggest that glucocorticosteroid contact allergy should be considered as a crucial clinical problem in patients with inflammatory dermatoses like CVLU, AD and CD.

KEY WORDS: contact allergy, glucocorticosteroids, venous leg ulcers, atopic dermatitis, contact dermatitis

INTRODUCTION

Contact allergy to topical glucocorticosteroids has been recognized as a problem of both clinical and therapeutic importance. It affects 0.5% to 5.8% of patients (1-4). The prevalence of contact allergy to these agents depends mainly on the type of dermatosis investigated, type of glucocorticosteroid screening markers used on patch testing and awareness of glucocorticosteroid contact allergy, thus resulting in variable data reported in the literature (1,4). Among the risk factors for developing delayed type of hypersensitivity to topical corticosteroids, chronic inflammatory skin diseases and patients presenting two or more positive patch test results and multiple medicament sensitivities seem to be most important (5,6). Patients suffering from chronic venous leg ulcers (CVLU), stasis dermatitis and contact dermatitis (CD) are also known as an increased risk group (2,7,8). Contact allergy in patients with atopic dermatitis (AD) affects up to 40% of cases, which has become an important clinical problem that may sometimes be difficult to recognize (9,10). AD patients seem to be a potential population for developing contact allergic reaction to glucocorticosteroids. Dooms-

Acta Dermatovenerol Croat
2008;16(2):72-78

Gossens and Degreef suggest that each case of CD resistant to glucocorticosteroids topical treatment should be considered as a hypersensitivity reaction to the medication applied (11). Moreover, according to observations reported from various clinical researches, the prevalence of contact allergy to glucocorticosteroids tends to increase (2,12,13). Recently, there was a very interesting and detailed discussion concerning the methodology of diagnostic procedures (1-3,7,8,14-22). Corticosteroid screening markers include at least tixocortol pivalate and budesonide (for corticosteroid cross-reaction groups A, B and D). This panel might be completed by a group C marker such as betamethasone-17-valerate or hydrocortisone-17-butyrate (1,2,18,22). Thomson *et al*. showed a combination of tixocortol pivalate and budesonide to detect more than 90% of contact allergy to steroids (8). Due to anti-inflammatory properties of corticosteroids, which may suppress allergic reaction at early readings, it is recommended to perform the verifying late reading on day 7 (3,16,20,22). The aim of this study was to evaluate the prevalence of contact allergy to glucocorticosteroids in patients with CVLU, AD and CD, and in a group of healthy individuals as well as to estimate differences between the study groups of patients considering contact and polyvalent allergy and allergic contact reaction to the specific allergens applied.

MATERIALS AND METHODS

Fifty CVLU patients, 30 AD patients, 30 CD patients and 30 healthy individuals were enrolled in the study. Patients with diabetes mellitus, hypertension and active stasis dermatitis or contact dermatitis were excluded from the study. In CVLU

Table 1. List of allergens tested in study groups (number and percentage of positive reactions)

Allergen and concentration (%)	50 CVLU patients (%)	30 AD patients (%)	30 CD patients (%)	30 healthy individuals (%)
Potassium dichromate (0.5)	3 (6%)	3 (10%)	6 (20%)	1 (3%)
Neomycin sulfate (20)	10 (20%)	0	4 (13%)	0
Thiuram mix (1)	0	0	1 (3%)	0
Paraphenylenediamine (1)	2 (4%)	1 (3%)	1 (3%)	0
Cobalt chloride (1)	3 (6%)	1 (3%)	3 (10%)	1 (3%)
Benzocaine (5)	2 (4%)	0	0	1 (3%)
Formaldehyde aq (1)	0	0	1 (3%)	0
Colophony (20)	3 (6%)	1 (3%)	2 (7%)	0
Clioquinol (5)	5 (10%)	0	0	0
Balsam of Peru (25)	19 (38%)	1 (3%)	1 (3%)	0
N-Isopropyl-N-phenyl-4-phenylenediamine (0.1)	1 (2%)	0	1 (3%)	0
Wool alcohols (30)	15 (30%)	2 (7%)	0	0
Mercapto mix (2)	4 (8%)	0	1 (3%)	0
Epoxy resin (1)	1 (2%)	0	0	0
Paraben mix (16)	10 (20%)	1 (3%)	0	0
4-tetr-butylphenol formaldehyde resin (1)	3 (6%)	0	0	0
Fragrance mix (8)	10 (20%)	3 (10%)	4 (13%)	0
Quaternium-15 (1)	0	0	0	0
Nickel sulfate (5)	4 (8%)	2 (7%)	10 (33%)	2 (7%)
Kathon/Euxyl/Grotan (0.01)	0	0	0	0
Mercaptobenzothiazole (2)	1 (2%)	0	0	0
Sesquiterpenelactone mix (0.1)	0	0	0	0
Primin (0.01)	1 (2%)	0	0	0
Tixocortol pivalate (1)	8 (16%)	1 (3%)	3 (10%)	0
Budesonide (0.01)	10 (20%)	0	2 (7%)	0
Betamethasone-17-valerate (1)	2 (4%)	0	1 (3%)	0
Glucocorticosteroids: sum	16 (40%)	1 (3%)	6 (20%)	0
Gentamicin sulfate (20)	2 (4%)	0	1 (3%)	0
Lanolin (pure)	1 (2%)	0	0	0
Eucerin (pure)	1 (2%)	0	0	0

CVLU, chronic venous leg ulcers; AD, atopic dermatitis; CD, contact dermatitis

Acta Dermatovenerol Croat
2008;16(2):72-78

group there were 38 (76%) female and 12 (24%) male patients, mean age 66.2 (range 48-81) years and mean duration of CVLU 7.2 years (range 6 months to 35 years. In AD group there were 22 (73%) female and 8 (27%) male patients, mean age 32.4 (range 18-58) years and mean duration of AD 16.8 (range 2-58) years. In CD group there were 22 (73%) female and 8 (27%) male patients, mean age 50.1 (range 24-71) years and mean duration of CD 6.4 (range 1-21) years. In the group of healthy individuals there were 12 (40%) female and 18 (60%) male subjects, mean age 33.9 (range 20-62) years. Clinical diagnosis of CVLU was verified by use of the clinical part of CEAP classification, color duplex ultrasound examination and ABPI (ankle brachial pressure index) determination. The diagnosis of AD was made according to Hanifin and Rajka criteria (23).

Patch testing

Patch tests were performed with the European standard series (TROLAB, Hermal, Germany) supplemented with glucocorticosteroids (tixocortol pivalate, budesonide, betamethasone-17-valerate), gentamicin (Chemotechnique Diagnostics, Sweden), and lanolin and eucerin as ointment vehicles (Hospital Farmacy, Poland) (Table 1). For patch testing, Finn Chambers on Scanpor (Epitest, Finland) were used. Results were recorded at 48 and 72 hour time points. For topical glucocorticosteroids the verifying readings were performed on day 7. According to ICDRG (International Contact Dermatitis Research Group), reactions evaluated as ++ and +++ were considered positive, and reactions evaluated as + as doubtful. Only ++ and +++ reactions were taken in consideration for further analysis.

Table 2. Prevalence of polyvalent allergy in CVLU, AD and CD patients

Patient group	Number of positive reactions in one patient	Prevalence (%)
CVLU	2	32.1
	3	17.9
	4	21.4
	5	10.7
	6	7.1
	7	3.6
	9	7.1
AD	2	17
	3	3
CD	2	16
	3	7
	4	7
	5	3

CVLU, chronic venous leg ulcers; AD, atopic dermatitis; CD, contact dermatitis

Ethics

The study was approved (opinion no. 503/02) by the Institutional Review Board, Poznan University of Medical Sciences.

Data analysis

Comparative evaluations of the prevalence of contact and polyvalent allergy as well as the prevalence of positive allergic reactions to standard allergens and glucocorticosteroids in the study groups of patients were performed with Mann-Whitney test and Fisher exact test. On statistical analysis, the STATISTICA version 6.0 and StatXact program version 4.0.1 were used.

RESULTS

In the group of CVLU patients positive patch tests results were recorded in 80% of patients and polyvalent allergy in 56% of cases. In the group of AD patients following results were obtained: positive patch tests results in 30% and polyvalent allergy in 20% of patients. In the group of CD patients allergic type of CD was detected in 80% and polyvalent allergy in 33% of patients. In the group of healthy individuals allergic contact reaction was observed in 17% of cases. Positive patch test results in our groups of patients are characterized in Table 1 and frequencies of multiply positive reactions (polyvalent allergies) are detailed in Table 2.

Contact and polyvalent allergy

The comparative evaluation of frequency of the contact and polyvalent allergy in our patients groups was performed. Considering contact allergy frequency, the obtained difference was statistically significant between CVLU patients and both AD patients ($p<0.0001$) and healthy individuals ($p=0$). Moreover, statistically significant difference was found between CD patients and both AD patients and healthy individuals (accordingly $p<0.001$ and $p<0.0001$). Considering polyvalent allergy frequency, the obtained difference was statistically significant between CVLU patients and both AD patients ($p<0.05$) and healthy individuals ($p=0$). Moreover, statistically significant difference was found between both AD and CD patients and healthy individuals (accordingly $p<0.05$ and $p<0.001$).

Acta Dermatovenerol Croat
2008;16(2):72-78

Table 3. Comparative evaluation of the prevalence of positive allergic reactions to standard allergens in study groups

Allergen	Study groups compared	*p*
Neomycin sulfate	CVLU patients/AD patients	<0.05
	CVLU patients/healthy individuals	<0.05
Balsam of Peru	CVLU patients/AD patients	<0.001
	CVLU patients/CD patients	<0.001
	CVLU patients/healthy individuals	<0.0001
Wool alcohols	CVLU patients/AD patients	<0.05
	CVLU patients/CD patients	<0.001
	CVLU patients/healthy individuals	<0.001
Paraben mix	CVLU patients/AD patients	<0.05
	CVLU patients/healthy individuals	<0.05
Nickel sulfate	CD patients/CVLU patients	<0.01
	CD patients/AD patients	<0.05
	CD patients/healthy individuals	<0.05

CVLU, chronic venous leg ulcers; AD, atopic dermatitis; CD, contact dermatitis

Positive allergic reactions to standard allergens and glucocorticosteroids

Comparative evaluation of positive allergic reactions frequency to standard allergens between examined groups of patients revealed statistically significant differences concerning the following allergens: neomycin sulphate, balsam of Peru, wool alcohols, paraben mix and nickel sulfate (Table 3). Comparisons of positive allergic reactions frequency to glucocorticosteroids in examined groups of patients were evaluated. Statistically significant differences were found considering tixocortol pivalate and budesonide (Table 4).

DISCUSSION

Contact allergy poses a problem in CVLU patients complicating the course of CVLU and making the disease difficult to diagnose. In many cases it is so because of a non-characteristic clinical picture. Moreover, the chronic nature of the problem and the wide spectrum of the potential causative therapeutic agents and occlusive dressings are factors that may favor both development of a delayed type of hypersensitivity and continuous changes in the allergen pattern. Another very important problem recorded in our study was the very high prevalence of polyvalent allergic reactions in CVLU patients. Our results confirmed those reported by other authors considering the high incidence of contact allergy and the role of the most common allergens in developing clinical symptoms of a delayed type of hypersensitivity in the study group of patients (24-27). Our study also demonstrated a very high incidence of contact allergy to glucocorticosteroids in CVLU patients (40%), which exceeded other literature reports (2,7,8,12,13,28). The use of tixocortol pivalate and budesonide combination and the verifying reading on day 7 enabled us to reduce the risk of omitting positive results. According to their allergic potential, corticosteroids have been divided into four groups from A to D (subdivided into D1 and D2 groups). Group A is known as the hydrocortisone type, group B as the triamcinolone acetonide type, group C as the betamethasone type, group D1 as betamethasone dipropionate type and group D2 as methylprednisolone aceponate type (1,2,18,22). They appear to have a high potential to cross-react within each group. However, cross-reactions between the groups are not common (22). We detected coexistence of positive results with tixocortol pivalate (group A representative) and budesonide (group B representative) in 3 (6%) cases and betamethasone-17-valerate (group D1 representative) with tixocortol pivalate or budesonide in 2 (4%) cases. The polyvalent glucocorticosteroid allergy in our group of CVLU patients was probably due to the chronic nature of venous insufficiency and leg ulcer processes as

Table 4. Comparative evaluation of the prevalence of contact allergy to glucocorticosteroids in study populations

Allergen	Study groups compared	*p*
Tixocortol pivalate	CVLU patients/healthy individuals	<0.05
Budesonide	CVLU patients/AD patients	<0.05
	CVLU patients/healthy individuals	<0.05

CVLU, chronic venous leg ulcers; AD, atopic dermatitis

well as to the time of exposure to different corticosteroids used for stasis dermatitis. These observations confirmed justifiability of the use of tixocortol pivalate and budesonide as corticosteroid screening markers. On the other hand, the additional betamethasone-17-valerate positive reaction was an important practical observation determining the possible treatment options, especially in patients with chronic dermatoses.

Allergic contact dermatitis in patients with AD affects up to 40% of cases, leading to an important clinical problem that may be difficult to recognize (9,10). The rate of 30% of positive patch tests results and the character of the most common contact allergens in our AD patients were quite similar to those reported elsewhere (24). Based on clinical trials, a group of risk factors for developing a delayed type of hypersensitivity to metals, especially nickel sulfate, in AD patients has been established, including female sex, young age and family or personal history of atopic diseases. In their epidemiological study, Mortz *et al*. detected a higher incidence of contact allergy in children with AD or bronchial asthma than in the group of control children without atopic diseases (29). Moreover, Berndt *et al*. emphasize the higher incidence of occupational contact dermatitis, especially to nickel sulfate, in adults with AD as compared with patients without this atopic skin disease (30). It is known that contact allergy to nickel sulfate may quite often coexist with allergy to other metals, especially cobalt chloride. The high prevalence of metal and fragrance allergens, common contact allergens as causative factors in AD patients, indicates the risk of contact allergy development and thus therapeutic difficulties. Moreover, the definite possibility of developing occupational contact dermatitis points to the necessity of proper patient education concerning the character of occupation chosen in young patients. Jappe *et al*. report on 0.87% budesonide and 1.14% hydrocortisone-17-butyrate positive patch test results in AD patients (10). Giordano-Labadie *et al*. did not observe contact allergy to glucocorticosteroids in any of their AD patients (9). Our study using both corticosteroid screening markers (tixocortol pivalate and budesonide) may offer another very important step in understanding the character of contact allergy in AD patients. Another clinically important observation made on the basis of our results is that in our AD patients we detected a high incidence of polyvalent allergy, which is a crucial factor for planning future topical treatment methods.

The prevalence of allergic contact reaction and contact allergy to the most common allergens recorded in CD patients is confirmed by literature data (30-34). Our results of contact allergy to glucocorticosteroids showed a very high incidence in comparison to the results reported by Boffa *et al*. (5.98%) (3). Similar to CVLU patients, we detected no case of isolated allergic reaction to betamethasone-17-valerate, but here again the application of tixocortol pivalate and budesonide enabled us to detect more cases of glucocorticosteroid contact allergy.

In the group of healthy individuals we obtained positive patch test results, mainly with metal allergens (17%). This observation proves the high potency of metal allergens in provoking contact allergy. Moreover, this can also be an evidence of “clinically mute” contact allergy, which in may subsequently develop into the symptomatic picture of allergic contact dermatitis.

Comparative evaluation of the prevalence of contact and polyvalent allergy as well as positive patch test results with both standard allergens and glucocorticosteroids revealed very interesting observations. CVLU patients should be classified as a group at the highest risk of developing contact allergy with the predominance of polyvalent allergic reactions and, which is very important from the clinical standpoint, they form a group at the highest risk of developing contact allergy to glucocorticosteroids. In AD patients, the problem of contact allergy and polyvalent allergy in some cases seems to be very important while complicating both clinical picture and therapeutic options. Differences between data on the prevalence of contact hypersensitivity to several allergens are due to the characteristics of inflammatory diseases. Additional studies of the pathophysiology of allergic contact reaction in CVLU patients as well as in AD patients are necessary and are planned to be performed at our Department of Dermatology and Allergic Diseases Diagnostic Center.

In view of the above, on the basis of our clinical results, we would like to emphasize that contact allergy in the study groups of patients poses a major problem, determining not only the course of the disease but also therapeutic possibilities and occupational implications. Moreover, we suggest that glucocorticosteroid contact allergy coexisting with the risk of cross-reactions between corticosteroid groups should be considered as a crucial clinical problem in patients with CVLU, AD and CD.

References

1. Matura M, Goossens A. Contact allergy to corticosteroids. Allergy 2000;55:698-704.
2. Wilkinson SM. Hypersensitivity to topical corticosteroids. Clin Exp Dermatol 1994;19:1-11.
3. Boffa MJ, Wilkinson SM, Beck MH. Screening for corticosteroid contact hypersensitivity. Contact Dermatitis 1995;33:149-51.
4. Isaksson M. Patch testing with corticosteroid mixes in Europe. A multicentre study of the EECDRG. Contact Dermatitis 2000;42:27-35.
5. Reitamo S, Lauerma AI, Stubb S, Kayhko K, Visa K, Forstrom L. Delayed hypersensitivity to topical corticosteroids. J Am Acad Dermatol 1986;14:583-9.
6. Dooms-Gossens A, Degreef H, Mariën KJC, Coopman SA. Contact allergy to corticosteroids: a frequent missed diagnosis? J Am Acad Dermatol 1989;21:538-43.
7. English JSC. Corticosteroid-induced contact dermatitis: a pragmatic approach. Clin Exp Dermatol 2000;25:261-4.
8. 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.
9. Giordano-Labadie E, Rance F, Pellegrin F, Bazex J, Dutau G, Schwarze HP. Frequency of contact allergy in children with atopic dermatitis: results of a prospective study of 137 cases. Contact Dermatitis 1999;40:192-5.
10. Jappe U, Schnuch A, Uter W. Frequency of sensitization to antimicrobials in patients with atopic eczema compared with nonatopic individuals: an analysis of multicentre surveillance data 1995-1999. Br J Dermatol 2003;149:87-93.
11. Dooms-Gossens A, Degreef H. Clinical aspects of contact allergy to corticosteroids. Dermatology 1994;189:54-8.
12. Reichert-Penetrat S, Barbaud A, Weber M, Schmutz JL. Ulceres de jambe. Explorations allergologiques dans 359 cas. Ann Dermatol Venereol 1999;126:131-5.
13. Wilkinson M, Cartwright P, English JSC. The significance of tixocortol-pivalate-positive patch tests in leg ulcer patients. Contact Dermatitis 1990;23:120-1.
14. Bjarnason B, Flosadottir E, Fischer T. Reactivity at edges of corticosteroid patch tests may be an indicator of a strong positive test response. Dermatology 1999;199:130-4.
15. Chowdhury MMU, Statham BN, Sansom JE, Foulds IS, English JSC, Podmore P, *et al*. Patch testing for corticosteroid allergy with low and high concentrations of tixocortol pivalate and budesonide. Contact Dermatitis 2002;46:311-2.
16. 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.
17. Isaksson M, Gruvberger B, Persson L, Bruze M. Stability of corticosteroid patch test preparation. Contact Dermatitis 2000;42:144-8.
18. Lepoittevin JP, Drieghe J, Dooms-Goossens A. Studies in patients with corticosteroid contact allergy. Arch Dermatol 1995;131:31-7.
19. Seukeran DC, Wilkinson SM, Beck MH. Patch testing to detect corticosteroid allergy: is it adequate? Contact Dermatitis 1997;36:127-30.
20. Wilkinson SM, Beck MH. Corticosteroid contact hypersensitivity: what vehicle and concentration? Contact Dermatitis 1996;34:305-8.
21. Wilkinson SM, English JSC. Hydrocortisone sensitivity: a prospective study of the value of tixocortol pivalate and hydrocortisone acetate as patch markers. Contact Dermatitis 1991;25:132-3.
22. Isaksson M. Corticosteroids. Dermatol Ther 2004;17:314-20.
23. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980;92:44-9.
24. Katsarou-Katsari A, Armenaka M, Katsenis K, Papageorgiou M, Katsambas A, Bareltzides A. Contact allergens in patients with leg ulcers. J Eur Acad Dermatol Venereol 1998;11:9-12.
25. Le Coz CJ, Scrivever Y, Santinelli F, Heid E. Sensibilisation de contact au cours des ulceres de jambe. Ann Dermatol Venereol 1998;125:694-9.
26. Wilson CL, Cameron J, Powell SM, Cherry G, Ryan TJ. High incidence of contact dermatitis in leg-ulcer patients – implications for management. Clin Exp Dermatol 1991;16:250-3.
27. Machet L, Couhe C, Perrinaud A, Hoarau C, Lorette G, Vaillant L. A high prevalence of

sensitisation still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and meta-analysis of 1975-2003 data. Br J Dermatol 2004;150:929-35.

28. Truchetet F. Batterie allergologique des ulceres de jambe. Ann Dermatol Venereol 1999;126:364-8.
29. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. Br J Dermatol 2001;144:523-32.
30. Berndt U, Hinnen U, Iliev D, Elsner P. Role of the atopy score and of single atopic features as risk for the development of hand eczema in trainee metal workers. Br J Dermatol 1999;140:922-4.
31. Kimber I, Dearman RJ. Allergic contact dermatitis: the cellular effectors. Contact Dermatitis 2002;46:1-5.
32. Streit M, Braathen L. Contact dermatitis: clinics and pathology. Acta Odontol Scand 2001;59:309-14.
33. Ulfgren AK, Klareskog L, Lindberg M. An immunohistochemical analysis of cytokine expression in allergic and irritant contact dermatitis. Acta Derm Venereol 2000;80:167-70.
34. Marks JG, Belsito DV, DeLeo VA, Fowler JF, Fransway AF, Maibach HI, *et al*. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. J Am Acad Dermatol 1998;38:911-8.

With Nivea on the air and sun; year 1937.
(from the collection of Mr. Zlatko Puntijar)