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ORIGINAL ARTICLE

Contact sensitization in patients with chronic wounds: Results of a prospective investigation

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Abstract

Background It is well known that patients with chronic wounds frequently acquire clinically relevant contact sensitizations to skin care products.
Objectives The aim of our study was to find out the actual frequency of contact sensitivities in patients with chronic wounds in Germany with particular attention to components of products used in modern wound therapy.
Methods We examined the results of a prospective clinical investigation on skin patch tests of patients with chronic wounds.
Results Altogether, 45 patients with chronic wounds were tested. In 25 (55.5%) of the examined patients, contact sensitization to at least one substance was detected. The most frequent contact sensitizations were to PVP-iodine (20%), balsam of Peru (15.6%) patients, fragrance mix (11.1%), colophony (8.8%) and potassium dichromate (6.7%). We also found sensitization to the wound dressings Varihesive™ (11.1%), Iruxol™ N (6.7%) and Comfeel™ (2.2%).
Conclusions We would like to propagate that therapists who are involved in wound treatment should also pay attention on the ingredients of applied modern wound dressings.

Introduction

Worldwide, about 2% of the adult population suffer from chronic wounds of different origins.[1] To support wound healing, those patients are treated with a variety of dressings and ointments. It is well known that patients with chronic wounds acquire more often contact sensitizations with clinical relevance compared with healthy populations.[2,3] Influencing factors may be the intrinsic genetic predisposition, lipophilic galenics, use of occlusion and the disrupted skin barrier with an increased permeability and inflammation of the skin upon which the wound care products are applied. The allergenic power and the concentration of different allergens in wound care products are important, but patients with chronic wounds acquire often sensitizations even against otherwise weak allergens.[4,5] Acquired sensitizations can lead to contact dermatitis, pain, impaired wound healing and prolongation of morbidity.[5–7] During the last years, the allergen spectrum found in patients with chronic wounds has changed. These changes are likely to depend on local wound care products and practice. Studies published within the past 10 years have shown for example an increasing frequency of rubber accelerator allergy, lanolin alcohol as well as to hydrogels.[2,8,9]

Although several investigators retrospectively analysed contact sensitizations, to our knowledge, there is yet only one recent prospective study in North America about contact sensitizations in patients with leg ulcers.[10] Even if modern wound care products are frequently used in these patients, only few studies report about their relevance for contact sensitizations. Therefore, the aim of our study was

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to find out the actual frequency of contact sensitivities in patients with chronic wounds in Germany with particular attention to components of products used in modern wound therapy.

Materials and methods

Patients

Between July 2004 and March 2005, altogether, 45 patients (27 men, mean age of 68.5 years; 18 women, mean age 63.4 years) with chronic wounds were included in the investigation. Wounds were defined as being chronic when existing at least 8 weeks. Patients were excluded if they received any topical or oral immunosuppressive therapy, therapeutic ultraviolet light exposition within the last 3 months, or if they had underwent a patch test within the last 6 months.

A physical examination was performed at the initial evaluation and consisted of the general appearance, evaluation of skin diseases, presence and severity of any dermatitis, description of the chronic wounds and evaluation of vascular diseases. A comprehensive medical history was performed with focus on the duration of the existing chronic wound and all used wound dressings. Informed consent was obtained from all patients.

Patch tests

Patch test substances were applied on hairless skin on the back for 24 or 48 h in 8-mm^2 Finn Chambers (Epitest™, Tuusula, Finland), which were taped with Fixomull™ stretch (BSN medical, Hamburg, Germany). Patch tests were performed with standard series, rubber series, resin/adhesive series of the German Contact Dermatitis Research Group and a self-composed panel of 14 allergens including antibiotics, corticosteroids, preserving agents and disinfectants (Table 1). In addition, a representative series of 10 modern wound care products from different companies were tested (Table 2), which consisted of two hydrocolloids (Varihesive™, Convatec, Munich, Germany and Comfeel™, Coloplast, Hamburg, Germany), an alginate (Algosteril™ Trionic, Johnson & Johnson, Norderstedt, Germany), a proteolytic enzyme (Iruxol™ N, Smith & Nephew, Lohfelden, Germany), a hydropolymer dressing (Tielle™, Johnson & Johnson), a silver and charcoal containing dressing (Actisorb™ silver, Johnson & Johnson), a foam dressing (Mepilex™, Mölnlycke Health Care, Erkrath, Germany), an antiseptic gel (Lavasept™, Fresenius, Bad Homburg, Germany), a hydrogel (Suprasorb™ G, Lohmann & Rauscher, Eiching, Germany) and a transparent polyurethane foil (Opsite™, Smith & Nephew).

Table 1 Tested chronic wound series

Allergen	Category
Benzalkonium chloride	Disinfectant
Benzoyl peroxide	Preservative
Benzyl alcohol	Preservative
Betamethasone-17-valerate	Corticosteroid
Budesonide	Corticosteroid
Chloracetamide	Preservative
Clobetasol-17-propionate	Corticosteroid
Framycetin sulphate	Antibiotic
Fusidine acid (sodium-sal)	Antibiotic
Gentamicin sulphate	Antibiotic
Hydrocortisone	Corticosteroid
Hydrocortisone-17-butyrate	Corticosteroid
PVP-iodine	Disinfectant
Triamcinolon-acetonide	Corticosteroid

Table 2 Self-composed series of modern wound care products

Wound care products	Positive test results
Varihesive™ thin	5 (11.1%)
Iruxol™ N	3 (6.7%)
Comfeel™	1 (2.2%)
Adaptic™	1 (2.2%)
Tielle™	0
Lavasept™ gel	0
Algosteril™ Trionic	0
Suprasorb™ G gel	0
Opsite™ foil	0
Actisorb™ silver	0
Mepilex™	0

Pieces of 4 × 4 cm edge length were applied with exception of Actisorb™ silver, which was tested 'as is' (edge length 6.5 × 9.5 cm) because it should not be dissected according to the manufacturers instruction. Patch test readings were performed at 48 h, 72 h and 96 h after patch test application. Patch tests were considered as positive if an at least positive reaction according to the criteria of the ICDRG was observed at 72 h or 96 h could be seen. The clinical relevance was determined by correlation of each positive patch test result with the medical history of the patient.

Statistics

The statistical analysis was done with Microsoft Excel 2000. $P < 0.05$ was regarded as significant.

Results

A total number of 45 patients with chronic wounds were investigated. The medical history revealed previous

episodes of chronic wounds in the past for 28 (62.2%) of these 45 patients. Altogether, 17 of the 45 patients developed the chronic wound for the first time, without a medical history of previous chronic wounds. Out of the 28 patients, 10 patients (35.7%) developed a chronic wound for the first time within the past 10 years, 5 patients (17.9%) within the past 20 years, 4 patients (14.3%) within the past 30 years, 1 patient (3.6%) within the past 40 years, 1 patient for more than 50 years ago and 5 patients (1.9%) within for more than 60 years ago. Two patients were not able to give relevant information about the duration of their chronic wounds. A total of 15 patients (33.3%) suffered from more than one chronic wound. The location of the chronic wounds was the lower legs in 44 (97.8%) of the patients. Only in 1 patient (2.2%) was the wound localized in the armpit. The primary aetiology of the chronic wounds was chronic venous insufficiency (CVI) in 26 patients (57.8%), peripheral arterial occlusive disease (PAOD) in 2 (4.4%) patients, combined CVI and PAOD in 4 (8.9%) patients, post-surgical wounds in 3 (6.7%), and neurotrophic ulcers in 2 (4.4%) patients. One patient (2.2%), respectively, suffered from vasculitis, third-degree skin burn, decubitus ulcer, livedo-vasculopathy, necrobiosis lipoidica non-diabeticorum, drug-induced thrombocytopenia, chronic lymphedema and ecthymata. Altogether, 18 patients (15.6%) had a thrombosis in the medical history, and 7 patients (15.6%) suffered from a diabetes mellitus type II. The duration of the chronic wounds was 2 to 480 (average 31.2) months.

The results of our study show that 25 (55.5%) patients had at least one contact sensitization. Among these, 14 (31.1%) patients had more than one contact sensitization, and 11 (24.4%) had one positive contact sensitization only. The average number of positive reactions was 1.8 for all tested patients. Regarding the patients with positive test reactions, we found an average of 3.3 positive test reactions in each individual. Sensitizations were found in 14 (51.8%) female patients and in 11 (61.1%) male patients.

The most common allergen found in our patients was PVP-iodine with 20% ($n = 9$) of all tested patients. Positive results to our self-composed series of modern wound care products were found for Varihesive in 11.1% ($n = 5$), Iruxol N ointment in 6.7% ($n = 3$) and Comfeel in 2.2% ($n = 1$) of all tested patients (Table 2). Other relevant contact sensitizations could be determined for balsam of Peru in 15.6% ($n = 7$), fragrance mix in 11.1% ($n = 5$), colophony in 8.8% ($n = 4$) and potassium dichromate in 6.7% ($n = 3$) of all patients with chronic wounds (Table 3). In addition, contact sensitizations were verified in 2 patients each (4.4%) for the following substances: nickel (II) sulphate, formaldehyde, paraben mix, gentamicin sulphate, cinnamon aldehyde, 1,3-diphenylguanidine, dispersion mix blue, bufexamac, wool alcohol (lanolin) and chloracetamide. Sensitizations in 1 patient (2.2%), respectively, for *para*-tertiary-butylphenol-formaldehyde *n*-Isopropyl-*n*-phenyl-*p*-phenylendiamin, *para*-tertiary-butylcatechine, *p*-phenylendiamine, 4,4-diaminodiphenylmethane, cobalt (II) chloride, benzocaine, framycetin sulphate, majantol, benzalconium chloride, propolis, mercaptobenzothiazole, methymethacrylate isoeugenol, composite mix, alpha-amylcinnamonaldehyde, hydroxicitronellal, geraniol, oak tree moss, benzoyl peroxide, quicksilver, turpentine, neomycin sulphate and cetyl stearyl alcohol.

Table 3 Most important allergens in our patients with chronic wounds

Contact allergens	Sensitization rates (%)
PVP-iodine	20.0
Balsam of Peru	15.6
Fragrance mix	11.1
Colophony	8.8
Potassium dichromate	6.7

For patients suffering from a chronic wound for 2 years or longer, we found an average of 3.5 sensitizations. An average of 3.2 sensitizations was found for patients with chronic wounds of < 2 years. We evaluated in 19 of 35 (54.3%) of the patients with an ulcer duration of 2 to 24 months at least one contact allergen compared with 6 of 10 patients (60.0%) for an ulcer duration of more than 24 months. The differences between these results do not reach statistically significance, suggesting that the persistence of chronic wounds and therefore the duration of treatment with the respective allergenic substances was not a relevant factor for the development of contact sensitizations.

Respectively, a single sensitization was found in 11 patients (24.4%) with an average duration of the chronic wound of 17.4 month. In 9 patients (20.0%), we verified two to five sensitizations. For those patients, the average duration of the chronic wound was 65.5 months. Finally, six to nine allergens were detected in 5 patients (11.1%) with an average duration of the chronic wound of 69.8 months. Therefore, patients with more than one sensitization tended to have a significantly longer history of chronic wound compared with patients with a single sensitization.

Discussion

Our data document the high frequency of contact sensitization in patients with chronic wounds. Worldwide, the quantity of positive patch test results in patients with

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chronic wounds ranges from 40.0% to 83.5%.[2,9,10] However, most of these studies were performed retrospectively and did not selectively analyse allergens in wound dressings. One exception was the prospective investigation by Saap *et al*. performed in North America with patients suffering from chronic leg ulcers.[10] In this investigation, 54 patients were prospectively recruited and patch tested with allergens consisted of the 2001 standard series from the NACDG and a self-created leg ulcer series of 52 allergens, including cosmetic allergens, topical drugs and wound care products such as transparent films, foams, hydrogels, hydrocolloids, alginates, composite dressings, topical antibiotics, antiseptics and topical corticosteroids. As the most important result, they described that 63% (n = 34) of all patients were sensitized to at least one allergen, a rate very similar to our own findings.[10] The design as well as the results of this study was similar to our investigation.

The use of modern wound care products provides several advantages for patients with chronic wounds such as improved healing, less pain, improved quality of life and lower nursing costs. In designing this investigation, we tried to utilize representative out of different classes of wound dressings and wound care products that are currently used worldwide. We attempted to determine which substance class tends to induce a higher frequency of contact sensitizations compared with others. Of the investigated wound dressings, Varihesive™, which is identical with Duoderm™ or Granuflex™ in other countries, had the highest frequency of sensitizations with 11% (n = 5) followed by Iruxol™ N ointment with 6.7% (n = 3) and Comfeel™ with 2.2% (n = 1). The frequency of 13.3% (n = 6) for sensitizations to hydrocolloid dressings is higher than in other recently published studies. For example, Machet *et al*. or Tavadia *et al*. found that none of their patients, and Lim *et al*. found that 2 of 44 patients, had a sensitization to hydrocolloid dressings only. We found no sensitizations to other tested wound care products such as foams or alginates.

As colophony is known to be an ingredient in Varihesive™, the high sensitization rate is not surprising. However, only four patients in our study showed an allergen sensitization to colophony, whereas we found five patients with an allergen sensitization to Varihesive™, indicating that there may be other allergens in Varihesive™ that we have not yet identified. Therefore, it has to be mentioned that colophony is a complex mixture of resin acids and neutral substances. Its composition varies with the species of coniferous trees from which it is obtained and also depends on the recovery process and storage. Today, colophony is frequently modified with various chemicals. The main allergenic compounds in colophony are oxidized acids of the abietic acid type.[11] Particularly, pentaerythriolester of hydrogenated rosin, one substance of content in some hydrocolloid dressings, is a derivative of colophony and as a tackifying agent can cause most of the sensitizations.[12,13] Testing to modified colophonium derivatives should therefore be performed in patients with allergic contact dermatitis from hydrocolloid dressings but a negative patch test result for colophony. To prevent the development of a contact a sensitization in patients with chronic wounds, highly potent allergens such as colophony should be avoided as a content material of modern wound dressings.

We were able to find for 4 of the 11 tested wound dressings contact sensitizations. Because colophony seems to be one of the most relevant allergens in wound dressings, we conclude that hydrocolloid dressings in our country as well as in other regions[13,14] have a higher risk than other modern wound dressings to cause contact sensitizations in patients with chronic wounds.

As shown in investigations performed before,[3,5,15,16] our data document a high rate of sensitizations to PVP-iodine (20%) and balsam of Peru (15.6%) in particular. In addition, the sensitization rates that were found in our study for fragrance mix, colophony and potassium dichromate were comparable with documented results of other studies from different countries.[2,10,17–20] As in other investigations, it was very difficult to assess the clinical relevance of these positive patch test results because sensitizations might have occurred several years before. In contrast to many other investigations, where neomycin was found to be an important contact allergen in patients with chronic wounds, we detect one single patient with a sensitization to this allergen in our collective only.[7] This might be due to the fact that neomycin or other antibiotics are not used regularly in patients with chronic wounds in Germany. These differences reveal the relevance of different local standards in the treatment for the results of patch tests.

In conclusion, we recommend patch tests with the currently used regionally different wound care products to allow patients the avoidance of identified allergens and to prevent the arise of contact sensitizations. However, primary prevention is more important. Topical application of substances with a high risk for induction of contact sensitization like PVP-iodine, balsam of Peru or antibiotics should be strictly restricted. Furthermore, a full declaration of the ingredients of wound care products is needed.

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