

Allergic contact dermatitis in venous leg ulcer patients

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Our aim was to determine the frequency and nature of contact sensitivity in venous leg ulcer patients in Lanarkshire. We performed patch testing with the European standard series, antimicrobials and medicaments on 200 patients referred to our leg ulcer clinics. Positive patch tests were found in 136 (68%) patients. Multiple allergies occurred in 102 (51%). The most frequent allergen groups were fragrances (30.5%), antimicrobials (19.5%), topical excipients (19.5%), rubber accelerators (13.5%) and topical corticosteroids (8%). We also found a high prevalence of positive patch tests to Intrasite[®] gel (9.5%) and Hioxyl[®] cream (8.5%), medicaments which are commonly used to treat leg ulcers in our area. Contact sensitivity is common in venous leg ulcer patients and has important implications for patient management. The allergens involved vary depending on local nursing practice. We suggest that all venous leg ulcer patients be patch tested with a locally relevant patch test series.

Key words: allergic contact dermatitis; epidemiology; hydrogels; leg ulcer; medicaments; patch testing; rubber; venous insufficiency. © Blackwell Munksgaard, 2003.

Accepted for publication 2 May 2003

Allergic contact dermatitis is a common complication of venous hypertension and leg ulceration (1–6), found in 67% of patients in a UK hospital series (7) and 60% in a community series (8). Contact allergy leads to dermatitis around leg ulcers, which contributes to the morbidity associated with leg ulcer disease. In animal models, active contact dermatitis impairs wound healing (9), and clinical experience suggests a similar effect in humans.

The pattern of allergens involved in allergic contact dermatitis affecting the skin around venous leg ulcers appears to be changing, and this change is likely to be determined by local wound-care practice. Studies published within the past 10 years have suggested an increasing frequency of rubber accelerator allergy (10), compared to earlier studies which highlighted aminoglycoside antibiotics, balsam of Peru (*Myroxylon Pereirae* resin) and lanolin alcohol as among the most frequent allergens in patients with venous hypertension and leg ulcers (6, 11–13). Another recent study showed a high frequency (4/36; 11%) of patients with venous insufficiency to have apparently allergic patch test reactions to hydrogels (3).

We aimed to find out the frequency of contact sensitivity and to determine which allergens are currently most frequent in venous leg ulcer patients in Lanarkshire.

Materials and Methods

We patch tested patients attending dermatology leg ulcer clinics in Lanarkshire (Monklands Hospital, Airdrie and Stonehouse Hospital, Stonehouse) between October 1997 and March 2001. All 200 new patients with a clinical diagnosis of venous or mixed venous and arterial leg ulcer were patch tested. Patients with leg ulcers due to other causes were excluded on clinical grounds or following biopsy. 117 of the 200 patients were female. The mean age of the patients was 70 years, range 34–95 years.

Patch testing

A patch test series based on the European standard series (14), antimicrobial and medicament series and a variety of commonly used topical leg ulcer treatments (including hydrating/desloughing agents and bandage materials) tested

Table 1. The Lanarkshire leg ulcer patch test series

Potassium dichromate 0.5%	Neomycin 20% pet.	Thiuram mix
PPD	Cobalt	Benzocaine 5% pet.
Colophonium 10% pet.	Quinoline mix	Balsam of Peru 25% pet.
PPD-black rubber	Lanolin alcohol 30% pet.	Mercapto mix
Epoxy resin	Paraben mix 15% pet.	PTBP
Fragrance mix	Sesquiterpene lactone mix	Quaternium-15 2% pet.
Nickel sulphate 5% pet.	Mercaptobenzothiazole	Primin
Chlorocresol 2% pet.	Triethanolamine	Benzalkonium chloride
Formaldehyde 2% aq.	MCI/MI	Betnovate [®] ointment
Tixocortol-17-pivalate 1% pet.	Clobetasol-17-propionate	Budesonide
Betamethasone	Triamcinolone	Alclomethasone
Dexamethasone-17-phosphate	Hydrocortisone-17-butyrate	1% hydrocortisone ointment
Sodium fusidate 2% pet.	Gentamicin	Hioxyl [®] cream
Chloramphenicol	Chlortetracycline	Framycetin
Trimovate [®] cream	Intrasite [®] gel	Flamazine [®] cream
Metronidazole cream	1% ichthammol zinc paste	Aqueous cream
Yellow soft paraffin	50:50 White soft paraffin: liquid paraffin	Diprobase [®] cream
E45 [®] cream	BHA	BHT
Triclosan	Sorbic acid	Chloroxylenol
Thimerosal	Imidazolodiny urea	Phenylmercuric acid
Chloroacetamide	Stearyl alcohol	Cetyl alcohol
2-Bromo-2-nitropropane-1,3-diol	Toluene sulphonamide foam resin	Propylene glycol
Sorbitan sesquioleate	Cetostearyl alcohol	Amerchol L-101
Isopropyl myristate	Phosphorus sesquisulphide	Release [®]
Granuflex [®]	Non-adherent dressing	Actisorb [®]
Sorbsan [®]	Inadine [®]	Ichthopaste [®] bandage
Viscopaste [®]	Coal tar bandage	Kling [®] bandage
Ortho wool [®] (lantor)	Crepe bandage	Elset [®] bandage
Coban [®] bandage	Cohfast [®]	Tielle [®]
Tegaderm [®]	Kaltostat [®]	Comfeel [®]
Lyfoam [®]		

MCI/MI = methylchloroisothiazolinone + Methylisothiazolinone; pet. = petrolatum; PPD = *para*-phenylenediamine; PTBP = 4-tert-butylphenol-formaldehyde resin; BHA = 2-tert-butyl-4-methoxyphenol; BHT = 2,6-ditert-butyl-4-cresol.

as is was developed. The Oxford series was used as a partial model (7). Patients were also tested to any additional topical treatments that they were using. This Lanarkshire leg ulcer patch test series continues to be modified: new topical agents becoming more frequently used are added, and

agents which are infrequently used or which do not produce positive patch test reactions are removed. The series used for the majority of this study period is listed in Table 1 and the allergens which have been removed or added to this series in Tables 2 and 3.

Table 2. Patch tests removed from the leg ulcer series in Table 1

Cobalt	PPD	Epoxy resin
Mercaptobenzothiazole	Primin	MCI/MI
Alclomethasone	Framycetin	1% ichthammol in zinc paste
50:50 White soft paraffin: liquid paraffin	Stearyl alcohol	Cetyl alcohol
Toluene sulfonamide foam resin	Phosphorus sesquisulphide	Granuflex [®]
Coal tar bandage	Cling [®] bandage	Crêpe bandage
Elset [®] bandage	Coban [®] bandage	Cohfast [®]
Tegaderm [®]		

MCI/MI = methylchloroisothiazolinone + Methylisothiazolinone; PPD = *para*-phenylenediamine.

Table 3. Patch tests added to the leg ulcer series in Table 1

Clobetasone (Eumovate [®] ung as is)	Oxytetracycline	Mupuricin
Nystatin 2%	Ethylenediamine HC	Ethylenediamine tetraacetic acid
Chlorhexidine	Polymyxin B sulphate	Bacitracin 20%
Nitrofluazone	Benzoyl peroxide	Eosin
Sorbitan monooleate	Phenylmercuric acetate	Diazolidinyl urea
Polyoxyethylene sorbitan monooleate	Duoderm [®]	Sterigel [®]

Patch test technique

Patch testing was conducted by the application of allergens to back skin on aluminium discs Finn Chambers[®] (Epitest Ltd, Oy, Tuusula, Finland) or plastic chambers (Chemotechnique Diagnostics, Malmö, Sweden) under Scanpor[®] tape (Alpharma AS, Norgesplaster, Vennesla, Norway). They were removed and read at day 2 (D2), with final readings at day 4 (D4). Reactions of + ICDRG (15) and above were regarded as positive.

Controls

Having found frequent positive patch test reactions to the non-standard agents Intrasisite[®] gel (Smith & Nephew Healthcare Ltd, Hull, UK), Hioxyl[®] cream (Adams Healthcare Ltd, Garforth, UK), Trimovate[®] cream (GlaxoSmith-Kline, Uxbridge, UK) and Flamazine[®] cream (Smith & Nephew Healthcare Ltd), we tested them on 200 control patients with no history of leg ulcer/venous disease, attending general patch test clinics.

Data analysis

The χ^2 -test was used when appropriate to compare proportions.

Results

136 (68%) of our patients showed at least 1 positive patch test reaction. Multiple reactions were common: 102 patients (51%) had at least 2 and 36 patients (18%) had 5 or more.

89% of positive reactions (460 of 514) were due to medicaments and regarded as of probable relevance to a current or previous lower leg dermatitis complicating the patient's leg ulceration.

The most frequent allergen groups and individual allergens are detailed in Tables 4 and 5.

For many of our patients, we cannot be certain of the relevance of identified positive patch test reactions. However, the following patients who were followed up after allergen avoidance advice illustrate the probable relevance of our findings.

Table 4. The most common contact allergens in our leg ulcer patients

Allergen	Number of patients with positive patch test reactions (%)
Fragrances	61 (30.5)
Fragrance mix	47
Balsam of Peru	29
Antimicrobials	39 (19.5)
Aminoglycosides	29
Sodium fusidate	9
Metronidazole	8
Chlortetracycline	4
Chloramphenicol	1
Topical excipients	39 (19.5)
Propylene glycol	4
Lanolin alcohol	33
Chlorocresol	2
Stearyl/cetyl/cetostearyl alcohol	6
Rubber accelerators	27 (13.5)
Thiuram	24
Mercapto mix	5
Topical corticosteroids	16 (8)
Betnovate [®] ointment	2
Tixocortol-17-pivalate	8
Clobetasol-17-propionate	1
Budesonide	3
Betamethasone	2
Dexamethasone	2
Hydrocortisone-17-butyrate	1

Case no. 1 – Rubber accelerator allergy

A 63-year-old woman with a 1-year history of 2 leg ulcers, with adjacent dermatitis, was referred to the leg ulcer clinic because of poor response to treatment. Prior to assessment, she was being treated with non-adherent (NA) dressing, Lyofoam[®] (SSL International plc, Knutsford, UK) and Setopress[®] (SSL International plc) (rubber free) bandaging. Patch testing showed positive reactions to thiuram, *para*-phenylenediamine (PPD) and nickel. She had regularly been in contact with rubber via gloves worn by the nursing staff who applied her treatment. A rubber-free treatment regime was started. Setopress[®] compression bandaging was continued, and topical corticosteroids were applied to the leg dermatitis. The dermatitis settled after 3 weeks and the ulcers healed after 6 weeks.

Table 5. Frequency of contact allergy to commonly used medicaments

Allergen	Positive PT reactions (%) in patients	Positive PT reactions (%) in controls	P
Intrasisite [®] gel	19 (9.5)	8 (4)	0.028
Hioxyl [®] cream	17 (8.5)	8 (4)	0.063
Trimovate [®] cream	13 (6.5)	7 (3.5)	0.17
Flamazine [®] cream	9 (4.5)	2 (1)	0.032

PT = patch test.

Case no. 2 – Intrasisite[®] gel allergy

A 79-year-old woman was referred with a 4-month history of 3 non-healing leg ulcers, the largest of which measured 13 × 15 mm, with adjacent dermatitis. Prior to assessment, she was being treated with Intrasisite[®] gel and Eurax[®] cream (Novartis Consumer Health, Horsham, UK). Patch testing showed positive reactions to Intrasisite[®] gel, Nu-Gel[®] (Johnson & Johnson Ltd, Maidenhead, UK), Flamazine[®] cream, tixocortol-17-pivalate 1% petrolatum and sodium fusidate 2% pet. She was treated with multilayer bandaging, NA dressing to the ulcer and 50:50 white soft paraffin:liquid paraffin to the surrounding skin. The ulcers healed after 9 weeks. In this case, both allergen avoidance and compression bandaging are likely to have contributed to ulcer healing.

Comment

The majority of venous leg ulcer patients attending specialist hospital and community clinics have positive patch test reactions (7, 8). The 68% with positive reactions, and the high frequency of patients with multiple allergens, that we found is similar to the findings of other centres (1–7).

Assessment of the relevance of positive patch test reactions can be difficult. In our study, the majority of positive patch tests were to medicaments used in the treatment of leg ulcers and are thus probably relevant. Contact sensitivity contributes to the dermatitis found around many leg ulcers and hence to associated morbidity. Our clinical experience, as illustrated in Case nos. 1 and 2, suggests that it may delay, or even prevent, healing. Further research to assess the effects of avoidance of allergens identified by patch testing on leg ulcer healing and on patient quality of life is required. The high proportion of patients with contact allergy in this and other studies suggests that all chronic venous leg ulcer patients, not only those with associated dermatitis, should be patch tested (16).

Our findings support other recent reports suggesting that the pattern of allergens involved in allergic contact dermatitis in venous leg ulcer patients changes in response to changes in nursing practice. We have confirmed Goopta & Powell's findings that rubber accelerator allergy has increased compared with earlier studies (4, 7, 8, 10). This increase may be because of the increased use of protective gloves by nursing staff or because elastic compression bandaging has become a standard practice in treating patients with leg ulcers in the past decade (16). The relative importance of these sources of rubber

accelerators requires further study. Allergen exposure would be reduced by nursing staff wearing vinyl rather than rubber gloves. The frequency of antimicrobial allergy has remained high over the last 25 years, but along with other recent reports we found that aminoglycoside allergy appears to be decreasing and fusidic acid allergy increasing (2). Compared with earlier reports, we found less allergy to lanolin alcohol (13, 17). We confirmed other studies showing that allergy to fragrance and balsam of Peru has remained common (2, 4, 13). In contrast, 2 recent reports found that allergy to fragrance and balsam of Peru was less common (7, 8). This difference may be due to local variation in topical application. Topical corticosteroid allergy was common (8%) in our leg ulcer patients and has not been reported in previous studies.

In our practice, commonly used medicaments for treating leg ulcers and the surrounding skin include Trimovate[®] cream, Hioxyl[®] cream, Flamazine[®] cream and hydrogels (Intrasisite[®] gel and the more newly introduced Sterigel[®] (SSL International plc)). Between 4.5% and 9.5% of our leg ulcer patients had positive reactions to these agents compared with 1–4% of our controls (Table 5). In the control group, 3.5% had positive patch tests to Trimovate[®] cream, and this may reflect the fairly common use of this agent. The percentage of positive reactions to Intrasisite[®] gel and Hioxyl[®] cream in the controls is higher than we expected and may suggest that these agents are irritant when tested as is. However, the increased percentage of positive reactions in the leg ulcer patients compared to the controls suggests that true positive reactions are occurring in the leg ulcer patients. There have been few studies investigating contact allergy to these medicaments. Gallenkemper et al., found that 4 of their 36 patients with chronic venous insufficiency had positive patch tests to hydrogels (3). In all of these patients, this was due to sensitization to propylene glycol 5%. In our study, we found 29 patients with positive patch tests to hydrogels (14 to Sterigel[®], 19 to Intrasisite[®] gel, 4 of these to both). Of these, 1 patient was patch test positive to propylene glycol 5% and 2 patients to propylene glycol 10%. We did not patch test our patients to modified carmellose polymer, the other constituent of Intrasisite[®] gel, and this may be the allergen in some of the remaining 26 patients. The frequency of positive patch tests to Hioxyl[®] cream was 8.5% (17/200), compared with 2 previous studies which found 15% (12/81) and 3% (2/59) (7, 8). In the majority of the cases of Hioxyl[®] sensitivity previously reported, the allergen was a component of Emulgade F[®]

(cetostearyl alcohol, sodium cetyl stearyl acid ester and the emulsifier Emulgin RO-40[®]) (7, 18). Of our patients who reacted to Hioxyl[®], 2 patients were sensitive to cetyl alcohol, 2 to stearyl alcohol and 2 to cetostearyl alcohol. We were not able to identify the allergens in the other 11 cases with positive patch tests to Hioxyl[®] cream. In our population, 13/200 (6.5%) had positive patch tests to Trimovate[®] cream. In 1 such patient, the allergen was chlorocresol and in 2 cetostearyl alcohol. We did not identify which component of Trimovate[®] cream was the sensitizer in the other patients, but we have added nystatin, oxytetracycline, clobetasone butyrate 0.05% and polyoxyethylene sorbitan monooleate to our series to investigate this further. 9/200 (4.5%) of our leg ulcer patients gave positive patch tests to Flamazine[®] cream. The sensitizer was propylene glycol in 2 cases and cetostearyl alcohol in 1 case. In the other patients, the allergens may have been 1% silver sulfadiazine or polysorbates, although 2 of our patients with positive patch tests to Flamazine[®] were tested to polyoxyethylene sorbitan monooleate (added to the patch test series) and this was negative in both. We are unaware of any previous studies which investigated for Trimovate[®] cream or Flamazine[®] cream sensitization in leg ulcer patients.

In contrast, some widely used types of dressings, such as alginates, NA, polyurethane foam and povidone iodine, result in extremely low rates of sensitization in our patients. These dressings might be good choices for patients without easy access to patch testing.

In summary, we have demonstrated that the frequency of positive patch tests in patients with leg ulcers is high. Our findings support other recent reports suggesting that the pattern of contact allergens in leg ulcer patients appears to be changing. By extending our patch test series to include commonly used agents, we have identified new allergens. We suggest that all leg ulcer patients should be patch tested with a specific, locally relevant, leg ulcer patch test series which will need to be continually updated.

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