

Contact sensitization in patients with chronic venous leg ulcers in Singapore

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Contact sensitization rates are high in patients with chronic venous leg ulcers. Allergic contact dermatitis poses a significant hindrance to the healing of the wounds. There are no published studies examining the rate of contact sensitization in Asian patients. Our objective was to determine the rate of contact sensitization in patients with chronic venous leg ulcer in Singapore and the variation in the common allergens based on local practices in comparison with Western countries. 44 patients were patch tested to the National Skin Centre standard series, steroid series, medicaments, topical Chinese medicaments, and to modern wound dressings used. The overall rate of contact sensitization was 61.4%. The common allergen groups were topical antibiotics (18.2%) and topical traditional Chinese medicaments (TTCM) (15.9%). Individually, colophony (11.3%), Saw Hong Choon skin ointment (Kam Bo Med, Hong Kong, Hong Kong) (11.3%), Balsam of Peru (9.1%), and povidone iodine (9.1%) were among the most frequent allergens. The sensitization rate among users of TTCM was notably high (41%). A high rate of contact sensitization was found in our study, similar to previous reports from the West. TTCM play a major role as possible allergens in our patients. In Asian patients, a history of its usage should be elicited, and patch testing should include the commonly used TTCM where possible.

Key words: allergic contact dermatitis; leg ulcers; stasis dermatitis; topical traditional Chinese medicaments © Blackwell Munksgaard 2007.

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Introduction

Leg ulcers are a chronic condition affecting 1–7% of the population older than 65 years (1). Allergic contact dermatitis is frequently observed among patients with venous stasis and leg ulcers (2–7), which poses a significant problem to the healing of leg ulcers and local skin care. There have been few, if any, published studies examining the incidence of contact sensitization in Asian patients suffering from chronic venous leg ulcers. Pattern of allergens involved constantly evolves according to the local wound care practice. Previous studies from the West highlight aminoglycoside antibiotics, Balsam of Peru, fragrance mix, and lanolin alcohol as among the most frequent allergens (1, 3, 5–7).

In Singapore, the use of topical traditional Chinese medicaments (TTCM) is common as self- or Chinese physician-directed remedies. This is especially so among the older generation of our population, who are also at higher risk of developing chronic venous leg ulcers. With the introduction of newer dressings in the treatment

of these patients, there have been corresponding reports of contact sensitization to these dressings (5, 8). We aimed to find out the rate of contact sensitization in patients with chronic venous leg ulcer in Singapore, and to determine the variation in the common allergens based on local practices in comparison with Western countries.

Materials and Methods

Eligible patients attending our clinic, the National Skin Centre (NSC), a tertiary dermatological referral centre, between October 2005 and April 2006 were patch tested. Patients with a clinical and/or histological diagnosis of chronic venous (or mixed venous and arterial) leg ulcers were recruited. Patients with leg ulcers due to other causes, on systemic immunosuppression or with contraindications to patch testing were excluded.

Allergens selected were based on our NSC standard series, steroid series, medicament series and topical Chinese medicament series (Table 1). The latter was developed based on the 10 most

Table 1. Patch test allergens

Allergen/concentration/vehicle	
4-tert-Butylphenol form resin 1% pet.	Balsam of Peru 25% pet.
4-Chloro-3-cresol (PCMC) 1% pet.	Colophony 20% pet.
Budesonide 0.1% pet.	Neomycin sulfate 20% pet.
Nickel sulfate 5% pet.	Paraben mix 16% pet.
4-Phenylenediamine (PPD) base 1% pet.	Potassium dichromate 0.5% pet.
Mercapto mix 2% pet.	Quinoline mix 6% pet.
Wool alcohols 30% pet.	Thiuram mix 1% pet.
Flavine 0.5% pet.	Epoxy resin 1% pet.
Fragrance mix 8% pet.	Mercaptobenzothiazole 2% pet.
Betamethasone-17-valerate 1% pet.	Tixocortol-21-pivalate 0.1% pet.
Sesquiterpene lactone mix 0.1% pet.	Hydroxyisohexyl cyclohexene carboxaldehyde (Lyril) 5% pet.
Methylchloroisothiazolinone (Kathon CG) 0.02% aq.	Methyldibromoglutaronitrile 0.3% pet.
Quaternium 15 (Dowicil 200) 1% pet.	2-Hydroxyethyl methacrylate 2% pet.
2-Hydroxypropyl acrylate 0.1% pet.	Ethyleneglycol dimethacrylate 2% pet.
Methyl methacrylate 2% pet.	Triethyleneglycol diacrylate 0.1% pet.
Alclometasone dipropionate 1% pet.	Beclomethasone dipropionate 1% eth.
Betamethasone sodium phosphate 2% NaCl	Clobetasol 17-propionate 2% eth.
Desoximetasone 2% eth.	Clobetasol 17-butyrate 2% pet.
Dexamethasone 1% eth.	Dexamethasone sodium phosphate 2% NaCl
Fludrocortisone acetate 1% pet.	Difluocortolone valearate 1% eth.
Flumethasone pivalate 1% eth.	Fluticasone propionate 1% pet.
Fluprednidene acetate 2% eth.	Fluprednidene 21-acetate 2% eth.
Flucinomide 2% pet.	Fluocinolone acetonide 2% pet.
Hydrocortisone acetate 1% eth.	Hydrocortisone 17-butyrate 1% eth.
Halometasone Monohydrate 1% eth.	Hydrocortisone alcohol 1% eth.
Prednisolone 2% eth.	Mometasone furoate 1% pet.
Triamcinolone 1% pet.	Triamcinolone acetonide 1% eth.
Benzalkonium chloride 0.1% aq.	Bacitracin 5% pet.
Caine mix III 10% pet.	2-Bromo-2-nitropropane-1,3-diol (Bronopol) 0.25% pet.
Cetrimide 0.1% aq.	Caine mix IV 10% pet.
Chlorhexidine diacetate 0.5% aq.	Chloramphenicol 5% pet.
Dichlorophene 1% pet.	Chlorhexidine digluconate 0.5% aq.
Gentamicin sulfate 20% pet.	Edinburgh University solution of lime 0.3% aq.
Mercury ammonium chloride 1% pet.	Miconazole 1% ysp
4-Chloro-3-xyleneol (PCMX) 0.5% pet.	Nitrofurazone 1% pet.
Povidone iodine as is	Polymyxin B sulfate 5% pet
Propylene glycol 5% pet.	Promethazine hydrochloride 1% pet.
Sulfanilamide 5% pet.	Streptomycin 2.5% aq.
Triclosan 2% pet.	Tetracycline 3% pet.
Fucidin as is	Cetylstearyl alcohol 20% pet.
Axe brand oil (Leung Kai Fook Co., Singapore, Singapore) as is*	Eagle brand medicated oil (Eagle Brand, Singapore, Singapore) 50% olive oil*
Green grass oil (Tai Tong Ah Co., Singapore) 20% olive oil*	Saw Hong Choon skin ointment as is*
Tiger balm 10% ysp*	Tiger oil (Haw Par Healthcare Singapore, Singapore) as is*
Tjin Koo Lin 20% olive oil*	White flower oil as is*
Wong Cheung Wah UI Oil (Wong Seng Heng Co., Penang, Malaysia) 5% olive oil*	Zhen Gu Shui as is*

pet., petrolatum; eth., ethanol; aq., aqueous; ysp, yellow soft paraffin.

*Topical Chinese medicaments series allergens.

commonly used TTCM by patients attending our clinic (9, 10). Modern wound dressings used in our leg ulcer clinic were patch tested as is with the micronized silver dressings moistened with sterile water (Table 2). Allergens were applied to back skin on Finn Chambers[®] (Epitest Ltd., Oy, Tuusula, Finland) under Airpore[®] tape (Qiagen Inc., Valencia, CA, USA). Standard allergens were obtained from Chemotechnique Diagnostics, Malmö, Sweden. The patch tests were removed after 2 days and read on day (D) 2 and/or D3. A further reading on D7 was done to detect delayed reactions (11). Readings of + (International Contact Dermatitis

Research Group recommendation) and above were taken as positive.

This study was approved by the local institutional ethics committee, and funding was provided by the National Medical Research Council Enabling Grant, Singapore.

Results

A total of 44 patients were tested with a mean age of 63 years (range 33–86 years, median 62.5 years). There was a slight male predominance (male: female ratio 1.2:1). The average duration of their leg ulcer was 43.8 months (range 2–480 months,

Table 2. Patch test allergens: wound dressings

Duoderm CGF [®]
Acticoat [®]
Iodosorb [®] powder
Aquacel AG [®]
Urgotul SSD [®] (Urgo, Chenove, France)
Intrasite [®] gel
Allevyn [®] (Smith & Nephew plc)

median 19.5 months). 61.4% (27 of 44) of our patients had at least 1 positive patch test reaction, with 31.8% (14 of 44) having multiple positive readings. The common individual allergens and allergen groups, where applicable, are listed in Table 3. Reviewing the clinical and the medication history, where possible, showed that 18.5% of reactions were of present relevance and 51.8% were of past relevance.

At the time of patch testing, 38.7% (17 of 44) of our patients were using or had used at least 1 TTCM, 6.8% (3 of 44) were unsure or unable to recall TTCM usage, and 54.5% (24 of 44) denied ever having used it. The sensitization rate among users (current and past) of TTCM was 41% (7 of 17). Most of these patients (5 of 7) had positive reactions to more than 1 TTCM, with a further 3 of the patients also having positive reactions to allergens other than TTCM.

Discussion

Together with the antimicrobials, our study clearly shows the importance of TTCM as contact allergens in our group of patients with chronic venous leg ulcers. The overall sensitization rate of 61.4% was in agreement with studies from previous centres (2–7).

The sample size of 44 patients may be small in comparison with some previous Western reports, but our findings show a clear trend with respect to the common sensitizers. The clinical relevance of the positive reactions are also notoriously difficult to establish in these group of patients due to the chronicity of the disease and the large number of potential contact sensitizers that patients are exposed to. In our group of patients, there was also a reluctance to admit the use of TTCM. This may stem from an unwillingness to show the use of alternative therapies to a physician trained in 'Western medicine'.

Our findings highlight the importance of taking the local and the patient's personal practices into context when assessing the possible allergens in a case of allergic contact dermatitis in patients with venous leg ulcer. As shown in Table 3, the commonest individual contact allergens in our series included colophony (11.3%), Saw Hong Choon

Table 3. The common contact allergens by groups and individually in our patients

Allergens	Sensitization rate as per cent of all patients (number of patients)
Topical excipients	9.1 (4)
Wool alcohol	6.8 (3)
Cetylstearyl alcohol	2.3 (1)
Fragrances	9.1 (4)
Balsam of Peru	9.1 (4)
Fragrance mix	4.5 (2)
Antimicrobials	18.2 (8)
Flavine	6.8 (3)
Neomycin	4.5 (2)
Chloramphenicol	2.3 (1)
Gentamicin	2.3 (1)
Sulfanilamide	2.3 (1)
Miconazole	2.3 (1)
Antiseptics	9.1 (4)
Povidone iodine	9.1 (4)
Edinburgh University solution of lime	2.3 (1)
Topical traditional Chinese medicaments	15.9 (7)
Saw Hong Choon skin ointment	11.3 (5)
Tjin Koo Lin	6.8 (3)
Tiger balm	6.8 (3)
Eagle brand oil	4.5 (2)
Green grass oil	4.5 (2)
White flower oil	4.5 (2)
Zhen Gu Shui	4.5 (2)
Tiger oil	2.3 (1)
Wong Cheung Wah UI oil	2.3 (1)
Wound dressings	9.1 (4)
Duoderm [®] CGF	4.5 (2)
Iodosorb [®] powder	2.3 (1)
Intrasite [®] gel	2.3 (1)
Corticosteroids	4.5 (2)
Budesonide	2.3 (1)
Tixocortol-21-Pivalate	2.3 (1)
Rubber accelerators	2.3 (1)
Thiuram mix	2.3 (1)
Various	
Colophony	11.3 (5)
Sesquiterpene lactone mix	2.3 (1)
4-Phenylenediamine (PPD)	9.1 (4)
Methylchloroisothiazolinone (Kathon CG)	2.3 (1)

Allergen groups are given in bold.

ointment (Kam Bo Med, Hong Kong, Hong Kong) (11.3%), Balsam of Peru (9.1%), povidone iodine (9.1%), 4-phenylenediamine (9.1%), Tiger balm (Haw Par Healthcare, Singapore) (6.8%), and Tjin Koo Lin (Chien Chi Tow Co., Singapore) (6.8%). Wool alcohols (6.8%) and flavine (6.8%) were fairly common as well. Conversely, in a recent meta-analysis on the common sensitizers in patients with leg ulcer, fragrance mix (cumulative sensitization rate of 18.8%), lanolin (17.5%), Balsam of Peru (25.4%), and aminoglycosides (13.9%) were cited (1). A rising trend of rubber accelerator allergy was noticed as well (5.5%–12.0%) (1, 3, 6). In contrast, our sensitization rates to these allergens, i.e. fragrance mix (4.5%), aminoglycosides

(4.5%), and rubber accelerators (2.3%), were comparatively low.

The high sensitization rate of TTCM (41%) among its users in our series was rather surprising. A previous study from our centre showed a sensitization rate of only 4.5% (4 of 89) when users were tested to the same panel of topical Chinese medicaments. The presence of large quantities of activated Langerhans cells in early stasis eczema skin may explain the high sensitization rate (12). High rates of cross-sensitivity among the TTCM and fragrance mix, Balsam of Peru, and colophony have been well reported. (9, 10, 13–15). As it is, the exact formulations of these TTCM are notoriously difficult to ascertain because of various reasons (10, 16). The ingredients of the 10 topical Chinese medicaments in our series have been previously described, as was the method by which the final concentration of each TTCM for patch testing arrived at (9). In that study, no irritant reaction was detected. However, irritant contact dermatitis to TTCM is not uncommon with reports associated with the use of Zhen Gu Shui (Guangxi Yulin, China) and White flower oil (Hoe Hin, Hong Kong) among others. The high sensitization rate to Saw Hong Choon ointment (11.3%) is surprising and has not been previously reported. This preparation contains salicylic acid 5% as its main ingredient, which under occlusion may be an irritant. In our study, 4 of the 5 positive reactions to Saw Hong Choon ointment remained positive at the D7 reading (data not shown), decreasing the possibility of an irritant reaction.

The sensitization rate to wound dressings as a group was 9.1%, similar to previous findings (3, 5). Previous isolated reports of allergic contact dermatitis from hydrocolloid dressings have implicated the presence of the pentaerythritol-esterified gum rosin, used as a tackifying agent, as the putative allergen (17, 18). This substance retains the sensitizing potential of colophony. We did not further patch test the 2 patients with positive reactions to Duoderm CGF[®] (Convatec, Princeton, USA) to the putative allergen although 1 of the cases showed cross-sensitivity to colophony. Positive reactions to hydrogels caused by sensitization to propylene glycol have been reported (3, 5). Our patient with a positive patch test to Intrasisite[®] gel (Smith & Nephew plc, Hull, UK) had a negative reaction to propylene glycol. Contact sensitization to cadexomer iodine (Iodosorb[®] powder; Smith & Nephew plc) has not been previously reported. Our case that had a positive reaction to Iodosorb[®] powder was previously on this dressing with failure to heal. Switching to a different dressing resulted in a good recovery. There were no reactions observed

with the micronized silver dressings (Acticoat[®]; Smith & Nephew plc, Aquacel AG[®]; Convatec).

The decrease in the use of prescribed topical antimicrobials containing neomycin in our centre may explain its surprisingly low sensitization rate (4.5%) in our study. The higher sensitization rate for flavine (6.8%) may be due to exposure to over the counter medicaments containing the compound by patients. Povidone iodine is a rare sensitizer, but has been reported in patients suffering from stasis eczema (4, 19). In our study, povidone iodine tested as is may be an irritant. In contrast to several other studies (3, 6, 20, 21), our sensitization rates to topical corticosteroids (4.5%) and rubber accelerators (2.3%) remain low.

In conclusion, contact sensitization in Asian patients with chronic venous leg ulcers has not been previously reported. Our results show that the sensitization rates are comparable with previous studies from the West. The striking difference, however, is in the pattern of allergens implicated in the causation of allergic contact dermatitis in our group of patients. TTCM play an important role as contact sensitizers in our study. We recommend that in Asian patients with chronic venous leg ulcers, history of TTCM usage should be elicited, and patch testing should include the commonly used TTCM where possible.

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