

Contact allergy in patients with chronic venous leg ulcers

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Contact allergy (CA) is prevalent in patients with chronic leg ulcers (CLUs) due to venous stasis¹ and may delay wound healing. Exposure to different ointments and wound dressings over time combined with occlusive bandaging may predispose to contact sensitization². The spectrum of allergens depends on wound care practices^{3,4} and studies on CA in patients with CLUs from Norway are lacking.

To determine the occurrence of CA in patients with CLUs, patch testing was performed with Leg Ulcer Series (LUS) containing 27 chemicals and five additional substances relevant to wound treatment: Caine mix 3 and 5, Hydrocortisone, IntraSite gel (propylene glycol 20%, Smith&Nephew) and Brulidine (dibrompropamidine 0.15%, Sanofi-aventis) (Supplementary table 1). A fraction of the patients (52/97) was also tested with European Baseline Series (EBS) (Supplementary table 2).

PATIENTS AND METHODS

Patients were recruited from the Department of Dermatology, Oslo University Hospital, Norway (autumn 2010 to spring 2013). Inclusion criteria were venous leg ulcers persisting for more than six weeks. Patients on current immunosuppressive therapy were excluded. The study was approved by the Regional Ethical Committee (2010/1023).

Patch testing was done according to standard guidelines⁵ with the LUS patch test and five additional substances (97 patients) and the EBS (52 patients). Test substances (Chemotechnique Diagnostics®) were applied to the upper back for 48H in Finn Chambers® (SmartPractice) on Scanpor® tape (Norgesplaster AS) and removed by the patients themselves. Readings were done on D3 according to the recommendation of the European Society of Contact Dermatitis (ESCD). Erythema only, without infiltration, were considered negative. When testing Brulidine and IntraSite gel, we used over the counter (OTC) preparations, and we did not control for reactions to the other ingredients these creams/gels contain.

Analysis of data were done in SPSS v21 (IMB Corp.).

RESULTS AND DISCUSSION

A total of 97 patients were tested (61 women, 36 men, median age 78 years, range 34-99 years). Mean duration of ulcer was 3.8 years (range six weeks to 40 years).

LUS patch test with 5 additional substances: positive patch test was detected in 31 of the 97 patients (32%). The most frequent allergens were Wood tar mix, benzalkonium chloride, fusidic acid, IntraSite gel, budesonide, and hydrocortisone-17-butyrate (Figure 1a). All these are relevant to wound treatment as they are constituents of standard wound dressing procedures in Norway. The findings are also in line with studies from other countries^{4,6-8}.

Benzalkonium chloride and fusidic acid are not recommended in chronic wound care but are widely used in primary care as constituents of preparations sold over the counter.

Benzalkonium chloride is often used in wet wipes, and our results suggest that antiseptic wipes should not be used in these patients. Five of the patients had an allergic reaction to IntraSite gel, but none of these had a positive reaction to the active ingredient propylene glycol when tested alone. This could be explained by a reaction to some other constituent of IntraSite gel for instance carboxymethyl cellulose which has been previously reported⁹, or by a difference in concentration of the test substances. IntraSite gel contains 20% propylene glycol while the concentration of the test substance in LUS is only 5% (supplementary table 1). Topical steroids are highly relevant due to the high prevalence of leg eczema in this patient group. CA towards budesonide and hydrocortisone-17-butyrate could indicate allergy against any topical steroid due to cross reactions, and user tests are needed to clarify. We chose to include Brulidine because it is widely used as an OTC preparation in Norway and CA is previously described¹⁰. Only two patients in our material had a positive reaction to Brulidine (+ and ++).

EBS patch test: twenty-seven of the 52 patients tested with EBS (52%) had positive reactions and *Myroxylon pereirae*, Fragrance mix and colophony were the most frequent allergens (Figure 1b) consistent with previous findings³. A reaction to wood tar mix could also indicate cross-sensitivity to colophonium.

40% of the patients with a positive patch test had one reaction, approximately 1/3 of the patients had two reactions, 10% had three reactions while 17% had 4 or more reactions simultaneously. When tested with both series some substances were tested twice, for instance Budesonide which occurs in both tests in the same concentration. Patients with a strong reaction tended to have consistent reactions, but weak reactions were not consistent. This could be explained by some weak reactions in fact being false positives.

One reading only is clearly a limitation to our study, and test readings on D5 and D7 would have been ideal not to miss any late reactions. A single reading on D3 was a practical compromise as our patient population was elderly, relatively immobile and with long travel distances.

Our findings confirm high prevalence of CA in patients with venous CLUs. These patients should be patch tested routinely with both LUS and EBS in order to exclude topical treatment that may delay wound healing.

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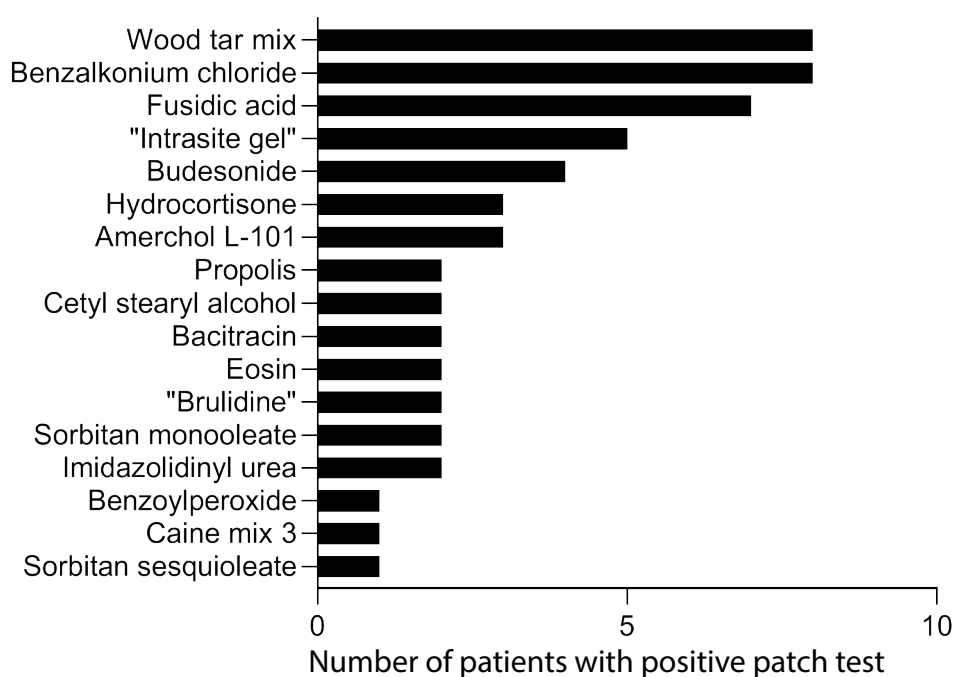
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Figure Legends:

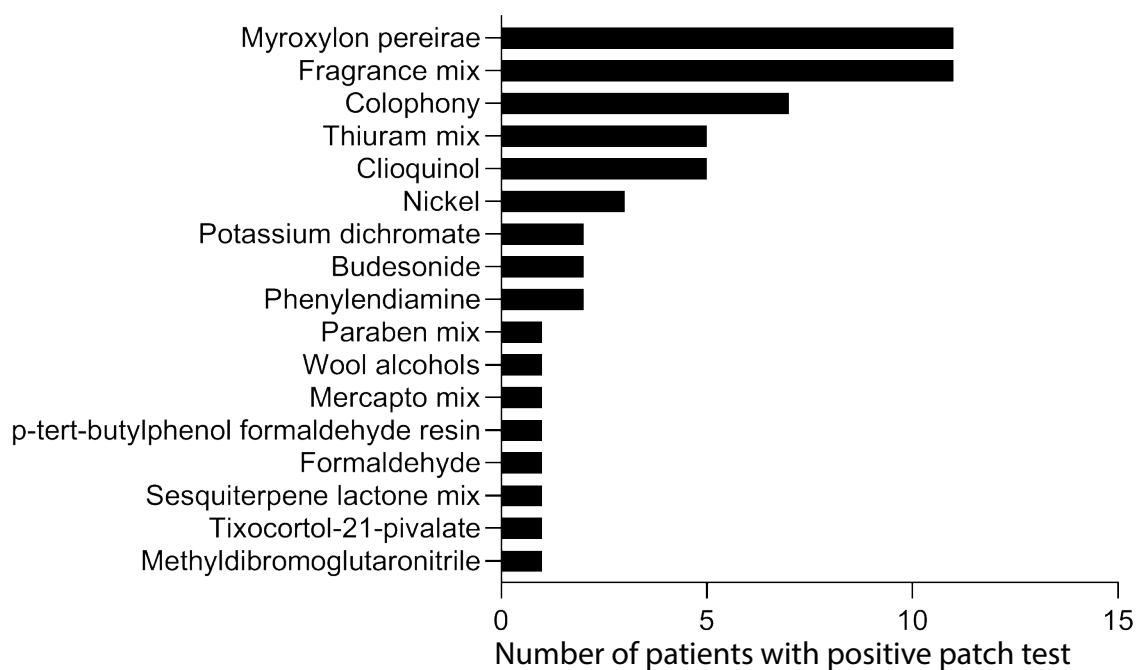
Figure 1: The most frequent contact allergens. Number of patients with positive test in (a) Leg Ulcer Series with the five additional substances and (b) European Baseline Series.

Figure 1

a



b



SUPPLEMENTARY TABLE 1. *Leg Ulcer Series patch test panel with five additional substances.*

Test Substance	CAS no	Conc (%)	Base	No of Reactions:		
				+	++	+++
Amerchol L-101	-	50.0	pet	3		
Fusidic acid sodium salt	751-94-0	2.0	pet	1	4	2
Chlorhexidine digluconate	18472-51-0	0.5	aq			
Benzalkonium chloride	8001-54-5	0.1	aq	3	5	
Nitrofurazone	59-87-0	1.0	pet			
Bacitracin	1405-87-4	5.0	pet	1		1
Cetearyl alcohol	67762-27-0	20.0	pet	1	1	
BHT	128-37-0	2.0	pet			
Chloramphenicol	56-75-7	5.0	pet			
Benzoylperoxide	94-36-0	1.0	pet	1		
Propylene Glycol	57-55-6	5.0	pet			
Propolis	85665-41-4	10.0	pet	2		
Thimerosal	54-64-8	0.1	pet			
Sorbic acid	110-44-1	2.0	pet			
Eosin	15086-94-9	5.0	pet	2		
p-Chloro-m-Cresol	59-50-7	1.0	pet			
Budesonide	51333-22-3	0.01	pet	2	1	1
Triethanolamine	102-71-6	2.0	pet			
Framycetin sulphate	4146-30-9	20.0	pet			
Sorbitan sesquioleate	8007-43-0	20.0	pet	1		
Tixocortol-21-pivalate	55560-96-8	0.1	pet			
Sorbitan oleate	1338-43-8	5.0	pet	2		

Phenyl mercuric acetate	62-38-4	0.01	aq			
Chloroacetamide	79-07-2	0.2	pet			
Diazolidinyl urea	78491-02-8	2.0	pet			
Imidazolidinyl urea	39236-46-9	2.0	pet		2	
Wood tar mix (Pine, beech, juniper, birch)	-	12.0	pet	1	6	1
Cain mix no III	94-09-7/61-12-1/ 136-47-0	10.0	pet			1
Cain mix no V	94-09-7/61-12-1/ 136-47-0	7.0	pet			
Hydrocortisone-17-butyrate	13609-67-1	1.0	alc	1	1	1
IntraSite gel	-	ud		1	2	2
Brulidine	-	ud		1	1	

Pet: petrolatum; aq: aqua; alc: alcohol; ud: undiluted

SUPPLEMENTARY TABLE 2. *European Baseline Series patch test panel.*

Test Substance	CAS no	Conc (%)	Base	No of Reactions:		
				+	++	+++
Potassium dichromate	7778-50-9	0.5	pet		2	
p-Phenylenediamine (PPD)	106-50-3	1.0	pet		2	
Thiuram-mix	94-37-1/97-77-8/ 137-26-8/97-74-5	1.0	pet	1	4	
Neomycin sulfate	1405-10-3	20.0	pet			
Cobalt (II) sulfate hexahydrate	7791-13-1	1.0	pet			
Caine mix no III	94-09-7/61-12-1/ 136-47-0	10.0	pet			
Nickel (II) sulfate hexahydrate	10101-97-0	5.0	pet	1	2	
2-Hydroxyethyl methacrylate	868-77-9	2.0	pet			
Colophonium	8050-09-7	20.0	pet	3	4	
Paraben mix	94-26-8/120-47-8/ 99-76-3/94-13-3	16.0	pet	1		
N-Isopropyl-N-phenyl-4-phenylendiamine	101-72-4	0.1	pet			
Lanolin alcohol	8027-33-6	30.0	pet		1	
Mercapto mix	102-77-2/120-78-5/ 95-33-0/149-30-4	2.0	pet			1
Epoxy resin/Bisphenol A	-	1.0	pet			
Myroxylon pereirae	-	25.0	pet	5	5	1
4-tert-Butylphenolformaldehyde resin (PTBP)	-	1.0	pet	1		
2-Mercaptobenzothiazole (MBT)	149-30-4	2.0	pet			
Formaldehyde	50-00-0	2.0	aq			1
Fragrance mix I	104-54-1/104-55-2/ 107-75-5/122-40-7/ 106-24-1/97-53-0/ 97-54-1/9000-50-4	8.0	pet	4	3	
Sesquiterpene lactone mix	546-43-0	0.1	pet		1	
Quaternium 15	51229-78-8	1.0	pet			
Propolis	85665-41-4	10.0	pet			

Methylisothiazolinone + Methylchlorisothiazolinone	55965-84-9	0.02	aq			
Budesonide	51333-22-3	0.01	pet		1	1
Tixocortol-21-pivalate	55560-96-8	0.1	pet		1	
Methyldibromo glutaronitrile	35691-65-7	0.5	pet		1	
Fragrance mix II	101-86-0/31906-04-4/4602-84-0/91-64-5/5392-40-5/106-22-9	14.0	pet	2	2	
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	31906-04-4	5.0	pet			
Methylisothiazolinone	2682-20-4	0.2	aq			
Textile Dye Mix	12222-75-2/2581-69-3/730-40-5/2872-52-8/3179-89-3/2832-40-8/68516-81-4/61951-51-7	6.6	pet			
Clioquinol	130-26-7	5.0	pet	3	2	

Pet: petrolatum; aq: aqua