

Contact sensitization in chronic venous insufficiency: modern wound dressings

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Patch tests with an expanded European standard series and 20 different wound dressings revealed sensitization in 78% of all (36) patients. The charts of allergens were headed by ointment bases (wool wax alcohols sensitization in 33% of all patients; Amerchol L-101 19.4%; cetearyl alcohol 13.9%; propylene glycol 8.3%), followed by plant resins/ethereal oils (balsam of Peru 22.2%; colophony 13.9%, fragrance mix 8.3%; propolis 5.6%) and topical antibiotics (neomycin sulfate 16.7%, chloramphenicol 13.9%), while usually common sensitizers like metal salts were not found as often (nickel sulfate 16.7%; potassium dichromate 13.9%; cobalt chloride 5.6%). Sensitization to modern wound dressings was found in 8.3% (3 cases) and was caused by propylene glycol as an ingredient of hydrogels; no sensitization was found to hydrocolloids, alginates or polyurethane foams. The overall sensitization rate in 2nd degree CVI was nearly as high as in 3rd degree CVI, but sensitization to ointments, their additives and topical antibiotics was significantly higher in 3rd degree CVI. Significant differences in sensitization frequencies to individual allergens were found between male and female patients. Our investigation points out the high risk of sensitization in 2nd as well as 3rd degree CVI, especially to ointment bases and active principles of topical drugs. Even wound dressings may cause allergic contact reactions.

Key words: chronic venous insufficiency (CVI); contact sensitization; wound dressings; medicaments; lanolin; cetearyl alcohol; propylene glycol; antibiotics; neomycin; chloramphenicol.
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Accepted for publication 22 January 1998

Previous investigations of the sensitization risk in chronic venous insufficiency or stasis dermatitis have shown a high sensitization rate of between 60 and 70% (1–10). All investigations point out the prominent rôle of ointments and their ingredients. Investigations of the sensitizing potential of modern wound dressings are few and focus only on single sensitizing agents (3, 4, 9). It was therefore the aim of our investigation to test modern wound dressings, in addition to the known top sensitizers, in chronic venous insufficiency.

Patients and Methods

Patients with signs of chronic venous insufficiency (CVI) presenting to the Dermatology Department of the University of Bonn over a 9-month period (July 1996–March 1997) were patch tested. The severity of the CVI was rated by the Widmer classification (11, 12) (Table 1). The allergens listed in Tables 2–4 were applied to the patients' backs for 2 days.

Top sensitizers in patients suffering from CVI or stasis dermatitis were defined by analysis of the literature (1–10) and selected for patch testing. The analysis resulted in a modified European standard series (Table 2) and other allergens (Table 3). In accordance with the object of the investigation, 20 modern wound dressings were chosen (Table 4) for additional patch testing. The results were read after 2 and 3 days (D), doubtful reactions after 4 days. Following ICDRG guidelines, reactions were rated as: – = no response, ?+ = erythema, + = erythema and oedema, ++ = palpable erythema, papular or vesicular reaction, and +++ = palpable

Table 1. Classification of Widmer (12): degrees of chronic venous insufficiency CVI

Degree	clinical signs
1st	edema and corona phlebectatica
2nd	skin changes such as dermatoliposclerosis and hyperpigmentation
3rd	previous or current venous ulcer

Table 2. Patch test allergens: European standard series allergens

Allergen	Concentration (%)	Vehicle	Sensitization rate as % of all patients	2nd degree CVI	3rd degree CVI	Female	Male
wool wax alcohols	30	pet.	33.3	10	41.7	37.5	25
balsam of Peru	25	pet.	22.2	40	16.7	21	25
neomycin sulfate	20	pet.	16.7	0	25	25	0
nickel sulfate	5	pet.	16.7	20	16.7	21	8.3
ceteryl alcohol	30	pet.	13.9	10	16.7	20.0	0
colophony	20	pet.	13.9	20	12.5	12.5	16.7
paraben mix	15	pet.	13.9	10	16.7	16.7	8.3
potassium dichromate	0.5	pet.	13.9	20	12.5	12.5	16.7
fragrance mix	8	pet.	8.3	10	8.3	8.3	8.3
mercury (II) amide chloride	1	pet.	8.3	20	4.2	8.3	8.3
n-isopropyl--n-phenyl-p-phenylenediamine	0.1	pet.	8.3	0	12.5	12.5	0
benzocaine	5	pet.	5.6	0	8.3	8.3	0
cobalt chloride	1	pet.	5.6	10	4.2	0	16.7
formaldehyde	1	aq.	5.6	10	4.2	4.2	8.3
mercapto mix	2	pet.	5.6	0	8.3	8.3	0
para-phenylenediamine	1	pet.	5.6	0	8.3	8.3	0
diaminodiphenylmethane	0.5	pet.	2.8	0	4.2	4.2	0
Kathon® CG	0.01	pet.	2.8	0	4.2	4.2	0
toluene sulfonamide/formaldehyde resin	10	pet.	2.8	0	4.2	4.2	0
chlorquinaldol	5	pet.	0	0	0	0	0
clioquinol	5	pet.	0	0	0	0	0
epoxy resin	1	pet.	0	0	0	0	0
Euxyl® K 400	0.5	pet.	0	0	0	0	0
p-tert. butylphenol-formaldehyde resin	1	pet.	0	0	0	0	0
thiuram mix	1	pet.	0	0	0	0	0
turpentine	10	pet.	0	0	0	0	0
petrolatum	as is		0	0	0	0	0

Table 3. Patch test allergens: other allergens

Allergen	Concentration (%)	Vehicle	Sensitization rate as % of all patients	2nd degree CVI	3rd degree CVI	Female	Male
Amerchol L-101	50	pet.	19.4	0	25	21	16.7
neomycin sulfate	20	pet.	16.7	0	25	25	0
nickel sulfate	5	pet.	16.7	20	16.7	21	8.3
ceteryl alcohol	30	pet.	13.9	10	16.7	20.9	0
chloramphenicol	5	pet.	13.9	10	16.7	16.7	8.3
phenyl mercury acetate	0.05	aq.	11.1	30	4.2	8.3	16.7
propylene glycol	5	pet.	8.3	10	8.3	12.5	0
chloracetamide	0.2	pet.	5.6	10	4.2	0	16.7
cobalt chloride	1	pet.	5.6	10	4.2	0	16.7
formaldehyde	1	aq.	5.6	10	4.2	4.2	8.3
framycetin	10	pet.	5.6	0	8.3	8.3	0
propolis	10	pet.	5.6	0	8.3	4.2	8.3
thimerosal	0.1	aq.	5.6	10	4.2	8.3	0
amalgam	5	pet.	2.8	10	0	0	8.3
benzalkonium chloride	0.1	pet.	2.8	0	4.2	4.2	0
chlorhexidine	0.5	aq.	2.8	10	0	4.2	0
Germall II	2	pet.	2.8	0	0	4.2	0
Germall 115	2	pet.	2.8	0	0	4.2	0
iodine	10	aq.	2.8	0	4.2	4.2	0
sodium fusidate	2	pet.	2.8	0	4.2	4.2	0
tert. butylhydroquinone	1	pet.	2.8	0	4.2	4.2	0
thiuram	0.25	pet.	2.8	0	4.2	4.2	0
wood tars	12	pet.	2.8	10	0	0	4.2
hydrocortisone-17-butyrate	0.1	pet.	0	0	0	0	0
triamcinolone	0.1	pet.	0	0	0	0	0

Table 4. Patch test allergens: dressing series

Allergen	Concentration	Vehicle	Sensitization rate as % of all patients	2nd degree CVI	3rd degree CVI	Female	Male
Intrasite [®] gel	as is	—	8.3	10	8.3	12.5	0
Varihesive [®] Hydrogel	as is	—	8.3	10	8.3	12.5	0
Hydrosorb [®] plus	as is	—	5.6	10	4.2	8.3	0
Allevyn [®]	as is	—	0	0	0	0	0
Biofilm [®] classic	as is	—	0	0	0	0	0
Comfeel [®] Paste	as is	—	0	0	0	0	0
ComfeelPlus FlexiblerWV [®]	as is	—	0	0	0	0	0
Cutinova [®] hydro	as is	—	0	0	0	0	0
Cutinova [®] foam	as is	—	0	0	0	0	0
Kaltostat [®]	as is	—	0	0	0	0	0
Mepithel [®]	as is	—	0	0	0	0	0
Mesalt [®]	as is	—	0	0	0	0	0
Oprigel [®]	as is	—	0	0	0	0	0
Sorbsan [®]	as is	—	0	0	0	0	0
Sureskin [®] standard	as is	—	0	0	0	0	0
Syspuderm [®]	as is	—	0	0	0	0	0
Tegasorb [®]	as is	—	0	0	0	0	0
Tenderwet [®]	as is	—	0	0	0	0	0
Tielle [®]	as is	—	0	0	0	0	0
Varihesive [®] E	as is	—	0	0	0	0	0

erythema, papular or vesicular, spreading reaction; only reactions greater or equal to + of crescendo-type were interpreted as allergic. We used standard allergens from Hermal[®]- and Hal[®], Germany; wound dressings were applied as is. For fixation, we used Finn Chambers[®] on Scanpor[®]; differing from this regime, wound dressings were fixed with Hayes – MED 5722P adhesive plaster (Hal[®]). Solid hydrocolloid-dressings were tested without chambers, calcium alginates were moistened with physiological saline solution. For concentrations and vehicles of the individual allergens see Tables 2 to 4.

Results

36 patients were tested; their average age was 64.5 years (range 37–89). 5.5% (2) had 1st degree CVI; 27.8% (10) 2nd degree and 66.7% (24) 3rd degree. 24 patients were female, average age 70.3 years (53–89); none had 1st degree CVI; 20.8% (5) had 2nd degree CVI and 79.2% (19) 3rd degree CVI. 12 patients were male; average age 52.8 years (37–68); 2 (16.7%) had 1st degree CVI, 41.7% (5) 2nd degree CVI and 41.7% (5) 3rd degree CVI. The average duration of CVI was about 21 years in all stages of CVI and varied from 1 to 56 years.

77.7% of all patients showed positive patch tests (female: 79.2%; male: 75%); the sensitization rates of these patients were in 2nd degree CVI: 90%, and in 3rd degree CVI: 75%. An average of 3.2 allergens elicited reactions in each patient (range 0–16) with nearly equal sensitization rates in 2nd (2.9) and 3rd degree CVI (3.5). The sensitization rates

to individual allergens in relation to sex and degree of CVI may be seen in Tables 2 to 4. In addition, we analyzed special groups of allergens. The results of this analysis are shown in Table 5. The allergen groups contained the following:

- emulsifiers: Amerchol L-101, cetearyl alcohol, propylene glycol;
- topical antibiotics: neomycin sulfate, framycetin, sodium fusidate, chloramphenicol;
- ethereal oils/plant resins: balsam of Peru, colophony, fragrance mix, turpentine, propolis;
- para-substituted and preservative agents: para-phenylenediamine, benzocaine, NIN-PPP, paraben mix, Euxyl[®] K 400, Kathon[®] CG, phenyl mercury acetate, benzalkonium chloride, chloroacetamide, thimerosal, tert.-butylhydroquinone;
- antiseptics: clioquinol, iodine, chlorhexidine, formaldehyde;
- preservatives and antiseptics : Euxyl[®] K 400, Kathon[®] CG, paraben mix, clioquinol, iodine, benzalkonium chloride, phenyl mercury acetate, chloroacetamide, Germall II, Germall 115, chlorhexidine, thimerosal.

Table 5. Sensitization to allergen groups

Allergen group	Sensitization rate (%)
ethereal oils/plant resins	36.1
para-substituted agents and preservatives	36.1
preservatives and antiseptics	33.3
emulsifiers	30.55
topical antibiotics	25
antiseptics	11

Table 6. Frequency of contact sensitization in chronic venous disease

Ref.	Publication date	No. patients	Frequency of sensitization (%)
(1)	1977		71.5
(2)	1979	103	63
(3)	1977	200	57
present work	1998	36	78
(4)	1988	59*	50.8
(6)	1977		57.8
(6)	1983	73	71.3
(7)	1985	100	69
(8)	1988	100	55
(10)	1991	81	67

* 20% without venous disease.

Discussion

36 patients may be too small a number on which to base valid statements, but analysed data should be able to show trends, especially in comparison to other investigations and regarding special points of interest. Our sensitization rate of about 70% is as high as those of other investigators (Table 6). Until now not analyzed, we registered nearly equal sensitization rates in 2nd degree CVI and 3rd degree. Bahmer (13) already proposed in 1987 that sensitization started early in CVI. He found large quantities of activated (HLA-DR-positive) cells in stasis dermatitis by immunohistological investigations. Our data may confirm his conclusions. Besides which, we found change of allergen distribution between 2nd and 3rd degree CVI and significant differences between female and male patients (Tables 2–4): female patients are significantly more often sensitized to ointments, emulsifiers, preservative agents and nickel sulfate than males. We attribute this phenomenon to different self-care behavior.

The widespread previous use of chloramphenicol in topical antimicrobial agents in Germany may explain the high sensitization rate of 13.9% in our patients. Sensitization rates as high as 43% to emulsifiers have been described by Pasche-Koo et al. (14) in 1994. Reports of sensitizations to sorbitan sesquiolate were made by Mallon & Powell (15) and Pasche-Koo et al. (14). Both traced the relevance of positive patch tests to medicaments and wound dressings used by the patients. Several investigators (cited in (3)) described contact sensitization to propylene glycol, the sensitization frequency being as high as 12%. Our results confirm these findings, which mirror the composition of modern ointments.

Unfortunately, emulsifiers like propylene glycol or sorbitan sesquiolate are often not declared in-

gredients of wound dressings. This may be harmful in case of sensitization to emulsifiers, when wound dressings without full declaration of ingredients are used. In our investigation, 4 patients showed allergic reactions to hydrogels caused by sensitization to propylene glycol. No hydrogel was labeled as containing propylene glycol. Few reports exist on contact sensitization to hydrocolloid dressings (16, 17), and these showed sensitization to the adhesive agents pentaerythritol ester (Pentalyn®) and a polyisobutylene derivative (Vistanex®). In our investigation, no positive patch tests were found to hydrocolloids, calcium alginates and PU-foams containing several different ingredients, including adhesives like acrylates and pentaerythritol ester.

In summary, we expect, like several other investigators (3, 6, 9, 10, 13, 14), full declaration of wound dressings and avoidance of the use of excipients, especially wool wax alcohols, fragrance, topical antibiotics and preservative agents, in chronic venous insufficiency. This is relevant even for mild forms of chronic venous insufficiency like stasis dermatitis.

Acknowledgements

We thank Mrs. Houska-Reimer, Mrs. Rothweiler and Mrs. Schumacher for technical assistance.

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