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Original Article

Value of patch testing with indigenous battery of allergens in shoe dermatitis

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Abstract

Objective To explore the potential allergens used in our domestic shoe industry and to determine the efficiency of indigenously prepared battery of allergens in shoe dermatitis.

Patients and methods A comprehensive list of 49 chemicals used in local processing and manufacturing of footwear was acquired from local sources. Potential irritants were excluded and a finished battery of 20 allergens relevant to our industrial environment was prepared by using standard techniques. Fifty patients and same number of control subjects were enrolled in the study for patch testing using Finn chambers and polyethylene IQ chambers. Results were read using standard protocol at 1 hour, 48 hours, 4th day, and 7th day. A pre tested, structured questionnaire was filled for each patient. Data were analyzed using SPSS version 12.0 for statistical analysis. Chi square test was applied for comparative analysis between patients and controls.

Results Out of 50 patients 33 (66%) were found to be allergic to 14 different chemicals present in indigenous test battery as opposed to 4 (8%) in control group (p<.0001, chi square test). Fifteen (30%) patients were reactive to additives used in processing and manufacturing of rubber. Eight (16%) patients were sensitive to agents used in tanning the leather. Four (8%) patients exhibited sensitivity to both leather and rubber and 6 (12%) patients were allergic to the chemicals present in resins, glues, plastics, dyes and metals. No reaction was observed at the site of application of blank chamber and vehicle.

Conclusion The indigenous battery is reliable, cost effective and flexible to adapt to changes in exposure and to introduction of new allergens in market. It would be prudent to recommend exploring the other industries like perfume, garments, and rubber, etc. on similar lines.

Key words
Shoes dermatitis, patch test, indigenous.

Introduction

Socks and lining of shoes were known to cause dermatitis since 1877, but it was not until 1930 when the patch test became more widely used that full potential of foot dermatitis became known.[1] With the discovery of leather, dyes, antioxidants, and rubber accelerators as possible causes of dermatitis, today contact allergy to shoes is recognized as one of the most important causes of dermatitis of the feet. The disability which results is great, despite accurate diagnosis and careful treatment and occurs during the period of greatest physical activity and emotional stress i.e. adolescence.

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The wearing of shoes creates an environment for the feet which especially favors development of contact dermatitis. For many hours daily we enclose our feet with leather, plastic, rubber, cloth, and adhesive containing hundreds of chemicals. Skin contact with these chemicals is maintained by the relative impermeability of the shoe. The accumulation of sweat increases the hydration of stratum corneum and a pronounced increase in percutaneous absorption. Researchers have shown that sweat leaches out chrome from leather, and it is probable that other chemicals are also released by sweat. Heat, pressure, and friction are other factors which promote the development of sensitivity.[2,3,4,5,6]

Although no population based studies of contact sensitization have been conducted in our country, a recent study from Norway has shown sensitization rates as high as 35.4% in women and 14.8% in men.[7] Population estimates of allergic contact dermatitis vary from 1.7% to 6%.[8,9] Potential allergens causing shoe dermatitis may vary from region to region. Therefore the cause of allergy may differ in populations.[10] The best way to assess the causes of allergy in our population would be to test an indigenously prepared battery of allergens, representative of the local shoe industry. This study was therefore undertaken to explore the potential allergens in our local shoe industry and to assess the efficacy of indigenously prepared battery of allergens in shoe dermatitis.

Patients and methods

The study was carried out at the department of dermatology, Combined Military Hospital, Kharian cantonment, Pakistan, from April 2002 to March 2003. Study was approved by the medical ethics and research committee of the hospital. Written informed consent was obtained from all the participating patients and controls.

Fifty consecutive patients with suspected allergic contact dermatitis from footwear were enrolled. The same number of subjects exposed to similar environments but without signs or symptoms of contact dermatitis was recruited as control. Patients with acute dermatitis, patients on systemic steroids, dermatoses at the site of application of patch test, and patients with tinea pedis confirmed on direct microscopy were excluded. A structured, pre tested questionnaire containing patch test results and data regarding patient's age, sex, occupation, duration of disease, weather variations, drug history, and predominant site of involvement was prepared and filled for each patient.

A survey of domestic shoe market was conducted and 49 chemicals used in processing and manufacturing of footwear were acquired from Bata shoe factory Lahore, Pakistan Council of Scientific and Industrial Research (PCSIR), Lahore, Tanneries from Qasur, and Plastic shoe factory, Lahore.

The chemicals procured from the above mentioned sources are enlisted in **Table 1**. Potential irritants and inert chemicals were excluded and a battery of 20 allergens was prepared by employing standard techniques.[11] The chemicals that were in granular or crystalline form were crushed to powder form with an electric grinder and sieved through a fine sieve to form uniform small sized particles. Accurate weighing of chemicals and petrolatum was done by using an electronic balance and mixing of the chemicals in appropriate vehicle was done with a mixer to get a homogeneous concentration. Allergens were placed in 5 ml propylene syringes and label was pasted on container with the name and concentration of substance. In the finished battery of 20 allergens, the concentrations of many chemicals were according to the European standard series

Table 1 Chemicals acquired from domestic shoe industry and included in battery.

Chemicals acquired from domestic shoe industry
1. Thiuram mix.
2. Mercaptobenzothiazole
3. Para-phenylenediamine.
4. Mercapto mix.
5. Para-phenylenediamine.
6. Potassium dichromate.
7. Colophony resin.
8. Epoxy resin.
9. Polyurethane (Desmocoll).
10. Poly spray to color rubber and plastic shoes (PVC)
11. Multi-glue (Ethyl acetate)
12. Azadiocarbonamide
13. Polyester resin
14. Diphenylguanidine (DPG)
15. Disperse yellow
16. Neoprene ethyl acetate used in rubber and glues
17. Nickel Sulphate
18. Formaldehyde
19. Shoe polish
20. Cobalt chloride
21. Sulphur used in vulcanization
22. Citric acid (STIR)
23. Santoguard (N Cyclohexyl -thiophthalimide)
24. Calcium carbonate
25. Dintro-pentamine-tetramine (DNO/DPT)
26. Calcium silicate (VN3)
27. Titanium dioxide (TIONA)
28. Bisulphonyl-hydrazide
29. Fat liquor
30. Turkey red oil
31. Cleansing solution for sanitary fittings
32. China clay
33. Zinc oxide
34. Discumyl per oxide (DCP)
35. Basozyme powder
36. Na-bisulphate
37. Na-formate
38. Tanni gum O.S
39. Tannigum PAK
40. Mimosa powder
41. Salochrome -26
42. Relugum –D
43. Relugum FFDG
44. Oxalic acid
45. Gelatin
46. Orapan bate
47. Neosyn FD
48. Disperse red
49. Lead sulphate

Cont…

Allergens in indiginous battery of shoe series
1. Neoprene Ethyl Acetate 0.25% in Pet
2. Polyurethane (Desmocoll) 1% in Pet
3. Mercaptobenzothiazole* 2% in Pet
4. Mercapto mix 2% in Pet
5. P- Phenylenediamine* 6% in Pet
6. Carba Mix 3% in Pet
7. Colophony (rosin)* 20% in Pet
8. Disperse yellow** 1% in pet
9. Thiuram Mix*1% in Pet
10. Poly spray to color rubber 1% in Pet
11. Multi glue Ethylacetate 1% in Pet
12. Nickel sulphate* 5% in Pet
13. Azadiocarbonamide** 0.5% in Pet
14. Polyester Resin 10% in Pet
15. Epoxy Resin. (P V C)* 1% in Pet
16. Cobalt Chloride 1% in Pet
17. Formaldehyde* I% in Aqua
18. Potassium dichromate* 0.5% in Pet
19. Sulphur 1% in Pet
20. Diphenyl guanidine* 1% in Pet

* Present in standard shoe series of Chemotechnique Diagnostics Sweden.[12]
** Present in extended shoe series.[26]

whereas the concentrations of the remaining chemicals not included in standard series were according to the Merck index.[11] Ten out of twenty chemicals of indigenous test battery are also present in standard shoe series of updated Product Catalogue of Chemotechnique Diagnostics, Sweden.[12] The chemicals present in indigenous shoe series are also enlisted in Table 1. There were certain allergens present in the standard shoe series of Chemotechnique Diagnostics, Sweden but were not included in the indigenous battery due to non availability in the local market and secondly they are not being used currently by leading footwear manufacturers (personal communication with chief chemist of Bata shoe factory).

Patch testing in 25 (50%) patients was carried out with the use of Finn chambers and in remaining 25 (50%), polyethylene I.Q. chambers of Chemotechnique Diagnostics were used and a similar pattern was observed for the control

Table 2 Interpretation of patch test results. Source: Adapted and modified from Drake Lynn *et al.*[13]

Reaction	*Grading*	*Interpretation*
0	No Reaction	No evidence of contact allergy
?	Weak erythema only	doubtful existence of contact allergy
1+	Erythema with edema covering at least 50% of patch test site	Possible contact allergy or false positive reaction.
2+	Erythema and papules or vesicles covering at least 50% of patch test site	Probable contact allergy
3+	Vesicles or bullae covering at least 50% of patch test site	Probable contact allergy or excited skin syndrome

subjects. The test material in petrolatum was expressed from syringe into the patch test appliance and panel was affixed on mid portion of back with scanpor paper tape or hypoallergenic tape in vertical row. In two female patients test panel was applied on outer aspect of upper arm. The patches remained in place for 48 hours and appropriate instructions were given to the patients. In all patients and control subjects, vehicle e.g. petrolatum and blank chambers were also applied along with test panel to asses reactions to vehicle or chamber. On removal, the sites of Finn/I.Q. chambers were marked with opaque ink and were evaluated after one hour and subsequent readings were recorded on 4th and 7th day. The patch test reactions were graded and interpreted as according to the prescribed guidelines of American Academy of Dermatology as shown in **Table 2**.[13]

Results

The mean age of patients was 38 years, range (15-65 years) and in the control group it was 34 years (range 20-48 years, $p>0.05$, chi square test). There were 39 (78%) male and 11 (22%) female patients. The mean duration of disease was 3.4 years, (range 1 month to 15 years).

In forty four patients (88%) predominant site of involvement was the dorsum of feet. Three (6%) patients had lesions on plantar aspect of feet and 3 (6%) patients presented with rash on dorsum and plantar surfaces of feet. Bilateral involvement was observed in 47 (94%) patients and dissemination to other sites was seen in 10 (20%) patients. Weather variations were recorded in 28 (56%) as these patients noticed improvements in winter with aggravation of rash in summer.

Thirty three (66%) patients showed positive patch test results to 14 different allergens present in shoe series as opposed to 4 (8%) subjects in control group ($p<0.0001$, chi square test). Out of 33 (66%) patch test positive patients, 17 (34%) patients exhibited reaction to more than one allergen whereas 16 (32%) patients were reactive to single allergen. The highest sensitization rate was found with additives used in processing and manufacturing of rubber as 15 (30%) patients were reactive to different rubber chemicals.

Eight (16%) patients were sensitive to agents used in tanning the leather. Four (8%) patients exhibited sensitivity to both leather and rubber and 6 (12%) patients were allergic to the chemicals present in resins, glues, plastics, dyes and metals.

As opposed to 33 (66%) patients, 4 (8%) subjects in control group showed sensitivity as 2 (4%) were allergic to carba mix and 2 (4%) to

Table 3 Patch test results.

Test allergens	*Patients (n=50)*	*Control n50*
Rubber	19 (38%)	2 (4%)
Leather	12 (24%)	0
Resins	3 (6%)	0
Metals	3 (6%)	2 (4%)
*Total	37 (74%)	4 (8%)

p<0.0001, chi square test.
* The total number of positive patients exceeds the actual number of 33 (66%) as 4 (8%) patients were reactive to both leather and rubber chemicals.

Table 4 Patch test results.

Test allergens	*Patients (n=50)*	*Control (n=50)*
(A) Rubber additives		
Carba mix	5(10%)	2 (4%)
Carba mix plus diphenylguanidine	5 (10 %)	0
p-Phenylenediamine	2 (4%)	0
Thiuram mix +disperse yellow	1 (2%)	0
Mercapto mix + Mercaptobenzothiazole	1 (2%)	0
Diphenylguanidine	1 (2%)	0
(B) Leather		
Potassium dichromate	6 (12 %)	0
Formaldehyde	1(2%)	0
Potassium dichromate +formaldehyde	1(2%)	0
(C) Leather and rubber		
Potassium dichromate+ Carba mix	3 (6%)	0
Potassium dichromate +Thiuram mix	1(2%)	0
(D) Resins		
Colophony resin	1 (2%)	0
Epoxy resin (P.V.C)	1 (2%)	0
Polyester resin+epoxy resin	1 (2%)	0
(E) Metals		
Nickel sulphate+Cobalt chloride	3 (6%)	2 (4%)
Total	33 (66%)	4 (8%)

P<0.0001, chi square test.

nickel sulphate (*p*<0.0001, chi square test). The patch test results are depicted in **Table 3**.

On analyzing the patch test result in **Table 4**, it is evident that among the rubber chemicals the main offending allergen is carba mix as overall 13 (26%) patients were sensitive to it as opposed to 2 (4%) subjects in control group (*p*<0.0001, chi square test). Five (10%) patients who were patch test positive to carba mix exhibited cross sensitivity to diphenylguanidine (DPG), which is one of the ingredients present in carba mix. This is followed by paraphenylenediamine to which 2 (4%) patients were sensitive. One patient each was reactive to thiuram mix and diphenylguanidine and one patient was allergic to mercapto mix with cross sensitivity to mercaptobenzothiazole (MBT).

After rubber chemicals second main allergen was potassium dichromate as 11 (22%) patients were sensitive to it and 4 (8%) of them also showed sensitivity to one of the rubber allergens.

The sensitivity to cobalt chloride was recorded in 3 (6%) patients and all showed cross sensitivity to either nickel sulphate or potassium dichromate. No reaction was observed to polyurethane, azadiocarbonamide, neoprene ethyl acetate, polyvinyl chloride spray for coloring rubber/plastic, and sulphur.

A total of 54 reactions to 14 different allergens were recorded of which 30 were (+1), 19 (+2), 5 doubtful (?) and in no patient +3 reaction was recorded. The total number of positive reactions exceeds the base number of patients because of cross sensitivity of patients to different allergens.

No reaction was observed at the site of application of blank chamber and vehicle. However in three patients and in the same number of control subjects non specific tape reaction was seen. Angry back syndrome was seen in one patient and persistence of reaction on 7th day was noted in 17 (34%) patients while 7 (14%) patients showed transient post inflammatory pigmentation.

Discussion

The present study has given a positive rate of 66% in suspected patients of contact dermatitis despite the fact that a number of allergens present in standard shoe series of Chemotechnique Diagnostics were excluded as they were not being used currently by domestic leading footwear manufacturers. There is a significant degree of variations in detecting the contact allergies in different series and a figure of 80 % is quoted as the percentage of contact allergies that American standard series can detect.[14] However a multi-center study involving 4824 patients with European patch test screening series the percentage of positive reactions varied from 37% to 73%.[15] Other researchers are of the opinion that if the yield of positive reaction is greater than 60% one is considered as too selective and in this perspective a sensitization rate of 30 to 60% is considered as appropriate.[16]

It is important to mention here that carba mix is neither included in European standard series nor in the standard shoe series and is therefore not routinely tested in footwear dermatitis[12] as it is regarded as a superfluous allergen in the presence of thiuram mix.[17] However, this view is not shared by North American Contact Dermatitis Research Group as both thiuram mix and carba mix are part of standard American series. A multi-center study by the North American Contact Dermatitis Group regarding the prevalence and relevance of common allergens has shown the relevance rate of carba mix as 71% and mercapto mix as 80%, respectively.[14]

Formaldehyde used in processing and tanning the leather to make it soft and water proof is important sensitizer in footwear, however in domestic industry formaldehyde or formaldehyde based resins are not commonly used as only two (4%) patients revealed sensitivity to it in present series.

Similarly the phenolic resins and thioureas, considered in the West as important source of sensitization, are used as adhesive in leather and water resistant rubber products. Although present in standard shoe series but were not included in indigenous battery as they were not being used currently by our major shoe manufacturers (personal communication with chief chemist of Bata shoe factory). These findings are comparable to an Indian study of footwear dermatitis with standard shoe series in which only one patient out of fifty was sensitive to p-tetra-butylphenolformaldehyde resin, whereas no reaction was observed with thioureas.[18]

Regional studies on shoe dermatitis using standard series give variable results. Some researchers show maximum reaction to rubber chemicals,[18,19] others have shown maximum sensitivity to chromates.[20,21] Other Pakistani studies also show variable results. In one study carried out at Mayo hospital Lahore 100 patients were patch tested with standard European and shoe series with a sensitivity rate of 72%. The commonest sensitizers were glues (34%) followed by neomycin (22%), nickel 14%, rubber chemicals (14%), leather (12%) and dyes (8%). The results of this study are at variance with our study.[22] A later study at the same center has shown somewhat variable results.[6] The variation may be due to difference in chemicals used in domestic shoe industry.

Nickel sulphate which is the commonest environmental sensitizer encountered in our patients as highlighted in another Mayo hospital study,[23] however its relevance in footwear dermatitis is questionable as in our study 3 (6%) patients were reactive to it compared to 2 (4%)

subjects in control group. This may represent sub clinical allergy to nickel among our population and positive reaction in shoe dermatitis may be the reflection of past relevance rather than true sensitization to footwear as such.

Our results correlate well with the socioeconomic conditions of population as most of the people use rubber and plastic footwear because they are economical, easily available and water proof. However the variations in individual allergen sensitivity in different series may be due to varying chemical composition of foot wear, individual susceptibility, and variation of screening series from place to place.

Considering the pattern of sensitivity to different chemicals in footwear, if we add suspected allergens of rubber, plastic and glue series along with standard shoe series the percentage of positive patch test reaction will certainly increase. This is evident by present study in which 15 (30%) patients reacted to chemicals like carba mix, mercapto mix and polyester resin which are not included in standard shoe series. This fact is supported by a study in which 24% additional contact allergies were diagnosable only by testing with allergens not found in the standard series.[15] Yet in another study it has been claimed that 5 to 23% of contact sensitivities can be detected by allergens not included in standard series.[24]

The addition of extra allergens will increase the cost of patch testing. Before starting this study the cost of standard shoe series by Chemotechnique diagnostics was Rs. 9,900. 00. And within a span of six months the price has jumped to Rs. 15,180. 00 and similarly the price of I.Q. chambers increased from Rs. 50 per strip of 10 chambers to Rs. 65. So the average cost of testing a patient with standard shoe series is Rs. 300.00. without consultation fee. Whereas in USA the average cost of applying a panel of 20 allergens is $82.[25]

Conclusion

Our results indicate that that the indigenous shoe battery is useful, cost effective, flexible and relevant for screening suspected patients with allergic contact dermatitis and is adaptable to changes in exposure and to introduction of new allergens in the market. It is therefore recommended that indigenous battery of allergens may be used as a primary screening tray and multi-center study may be conducted to make it more perfect. It would be judicious to explore the other industries like perfume, garments, and rubber, etc. on similar lines.

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