

Correlation between lesion site and concentration of dimethyl fumarate in different parts of shoes in patients with contact dermatitis caused by dimethyl fumarate in footwear

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Summary

Background. Dimethyl fumarate (DMF) has been identified as being responsible for an outbreak of shoe contact dermatitis in Europe. All reported cases to date have involved the dorsa of the toes and the dorsa of the feet, sometimes in association with other areas.

Objectives. To establish a correlation between the site of the lesions and the concentration of DMF in different parts of the footwear from patients suffering from shoe contact dermatitis.

Methods. We performed a retrospective study of 8 patients with shoe contact dermatitis caused by DMF. Clinical data and patch test results obtained with DMF were recorded. The contents of DMF in different parts of eight samples of shoes involved were analysed with gas chromatography–mass spectrometry.

Results. The chemical analysis of all samples studied showed the presence of DMF, both in the uppers and the soles of the shoes. A clinical–analytical correlation was found in all cases. The presence of DMF in a child's boot was detected 1 year after withdrawal of the sachet with DMF from the shoe box.

Conclusions. A correlation exists between the concentrations of DMF in the different parts of the shoe and the localization of the lesions. Although DMF is a volatile substance, it can remain impregnated in shoes for a long period of time.

Key words: contact dermatitis; dimethyl fumarate; patch test; shoe.

Dimethyl fumarate (DMF), a fumaric acid ester, is a substance that has been used as a preservative in anti-humidity sachets during the transport of furniture and footwear (1–3). Its irritant capacity when in contact with the skin and its great ability to sensitize have been amply demonstrated (4). There have recently been two outbreaks of severe contact dermatitis related to the

presence of DMF in furniture and footwear (1–9). We have seen several cases of contact dermatitis resulting from the presence of DMF in shoes, and have established that, although it can affect any part of the foot, the dorsum of the foot and the dorsa of the toes are more likely to be involved. This led us to question whether the causative factors include a greater concentration of DMF in the area of the shoe in contact with the dorsum of the foot. Accordingly, the concentrations of DMF in different parts of the shoes causing contact dermatitis were determined with gas chromatography combined with mass spectrometry. We then attempted to correlate the DMF concentrations with the sites of the lesions on the feet.

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Materials and Methods

Patients

Eight patients suffering from shoe contact dermatitis caused by DMF were studied at the dermatology departments of two Spanish hospitals, the Hospital General Universitario de Alicante and the Hospital Universitario Insular de Gran Canaria. All patients were patch tested with the baseline GEIDAC series of the Spanish Contact Dermatitis Research Group, the Chemotechnique® shoe series, and DMF at 0.01% in petrolatum (Allergeaze Marti-Tor®) or prepared by the pharmacy department of the Hospital General Universitario de Alicante. Shoe component (textile) extracts 10% in water and also in ethanol were patch tested in 6 patients. Readings were taken at D2 and D4, with the evaluation criteria (+, ++, and +++) recommended by the International Contact Dermatitis Research Group. The variables recorded for each patient were age, sex, site of the lesions, patch test results, and type of footwear involved. The patients were divided into three groups according to the site of the lesion: (i) patients who had greater involvement on the dorsa of the feet (including the toes); (ii) patients whose symptoms were mainly located on the soles of the feet; and (iii) patients who had involvement of both the soles and the dorsa of the foot.

Conservation of the samples prior to analysis

The shoes were all being sold in boxes containing anti-humidity sachets. Six of the eight pairs of shoes were taken out of their boxes, immediately placed in a plastic bag, and stored for later analysis. The other two were left in the shoe boxes in which they had been sold, after the suspicious anti-humidity sachets had been taken out. One of these was a boy's boot, and the other one had been analysed 1 year before in a Swedish laboratory, where they obtained two DMF measurements of 16 and 43 ppm; this has already been the subject of a publication (8). We are unaware of whether the sample analysed corresponded to the upper or the sole of the shoe. A measurement was also made of the DMF concentration in a piece of cardboard that was present in the shoe box belonging to patient number 1.

Chemical analysis

The determination of DMF was made by the Research Technical Services department of Alicante University. The samples were prepared following the same method used by the Department of Occupational and Environmental

Dermatology of Malmö University Hospital (8). The sample was prepared by extracting two samples of 0.5–1 g from each shoe, one from the front part of the upper, and the other from the front part of the sole (8). Then, 5 ml of ethyl acetate was added to each sample, which was then extracted and sonicated in an ultrasound bath for 5 min. The extract was then concentrated with a rotary evaporator to a volume of 1 ml. The DMF was analysed with an Agilent 5973N low-resolution mass spectrometer with a quadrupole analyser coupled to an Agilent 6890N gas chromatograph. The chromatographic column used was an HP-5MSI of length 30 m and internal diameter 0.25 mm. The electron energy used for ionization was 70 eV.

Results

Symptoms and patch tests

Of the 8 patients with shoe-induced contact dermatitis caused by DMF, 7 were adults and 1 was a boy. The lesions were mainly on the dorsa of the feet in 5 of the 8 patients (cases 1, 2, 3, 5, and 6), on the soles of the feet in 1 patient (case 7), and on both the dorsa and the soles of the feet in 2 patients (cases 4 and 8). All except 1 of the adults had a positive reaction to DMF at 0.01% pet. Patient 7 had negative patch test results with the baseline GEIDAC series, Chemotechnique® shoe series (Vellinge, Sweden), and DMF at 0.01%; this patient's own shoes were not tested. The boy showed an immediate contact reaction after the first exposure to some new boots contaminated with DMF. The above-mentioned patch tests in this boy, including his own boots, gave negative results, and he was deemed to have non-immunological contact urticaria. Half (3/6) of the patients patch-tested with samples from their own shoes showed intensely positive reactions.

Chemical analysis

In all eight shoes analysed, we were able to demonstrate the presence of DMF, both in the upper and in the sole (Table 1). The gas chromatography–mass spectrometry analysis demonstrated the presence of DMF in amounts ranging from 15.6 to 644.3 ppm. Large variations were seen in the concentration of DMF between the two parts of the shoe studied. In most samples (5/8), the concentration of DMF in the upper was much greater than that in the sole. In one shoe (sample 6), the concentration in the upper was seven-fold that in the sole. In only two of the eight shoes was the concentration greater in the sole (samples 7 and 8). In samples 4 and 8, no large variations were found in the concentration of DMF between the

Table 1. Epidemiological and clinical characteristics, patch test results, type of footwear, type of sample, and concentration of dimethyl fumarate (DMF)

Patient number	Sex	Age	Localization of the lesions	Patch test with DMF 0.01%	Patch test with patient's sample	Type of footwear	Footwear sample	DMF mg/kg (ppm)
Patient 1	F	58 years	Dorsa of feet	Positive	Positive	Lady's shoe	Sample 1 Upper Sole	204.6 96.8 17.68
Patient 2	F	45 years	Dorsa of toes	Positive	Negative	Lady's shoe	Cardboard Sample 2 Upper Sole	238.38 79.7
Patient 3	F	15 years	Dorsa of feet	Positive	Positive	Lady's shoe	Sample 3 Upper Sole	69.5 27.3
Patient 4	F	21 years	Dorsa of toes and soles	Positive	Negative	Lady's shoe	Sample 4 Upper Sole	65.2 39.3
Patient 5	F	72 years	Dorsa of feet	Positive	Positive	Lady's boot	Sample 5 Upper Sole	644.3 133.7
Patient 6	M	17 months	Dorsa of feet	Negative	Negative	Boy's boot	Sample 6 Upper Sole	165.4 23.4
Patient 7	M	36 years	Soles of feet	Negative	Not done	Man's slipper	Sample 7 Upper Sole	22.6 31.2
Patient 8	F	33 years	Dorsa of feet and soles	Positive	Not done	Lady's shoe	Sample 8 Upper Sole	18.4 20.7

F, female; M, male.

upper and the sole. In the piece of cardboard from one of the shoe boxes (sample 1), we detected an amount of DMF (17.68 ppm) that was much lower than that found in the different parts of the shoes (upper and sole), but similar to that detected in other samples studied.

Correlation between the symptoms and the concentration of DMF

Table 1 shows the correlation between the concentrations of DMF in the different parts of the footwear and the sites of the lesions in the patients.

Discussion

DMF is usually commercially available as a crystalline powder or white granules. It has been placed in sachets inside furniture or clothes as well as in shoe boxes. DMF has recently been implicated in microepidemics of contact dermatitis in persons who have purchased a sofa or shoes preserved with these sachets. It has been suggested that DMF may pass from the sofa or shoes because of its volatile nature (8, 10, 11), and in circumstances of extreme heat during transport it might evaporate and be deposited on all areas of the shoe while it remains in the box. Later, body

temperature and sweating could facilitate the release of DMF and thus increase exposure, causing irritation and inducing sensitization.

We were able to determine the presence of DMF in the piece of cardboard inside one of the shoe boxes. This showed us not only that the substance impregnated the surface of the shoes but also that it could accumulate inside the box where it was used. However, the concentration of DMF in the cardboard was less than that found in the shoe, indicating that not all of the materials could fix DMF with the same affinity.

We suspected that the dorsa of the feet and the toes would almost always be involved in patients with contact dermatitis caused by DMF, and we have now seen that 21 of the cases of contact dermatitis caused by DMF so far published (3, 8, 12, 13) have all experienced involvement of the dorsa of the feet, either exclusively or in association with other sites. Although this could be explained by anatomical (thinner skin on the top of the foot than on the bottom) or physical (area subject to greater sweating and/or rubbing) differences, we have now determined that it is at least partly attributable to a greater concentration of DMF in the top part of the shoe. This, therefore, results in this part of the foot being more

susceptible to acute irritant contact dermatitis, as well as sensitization and development of eczema. Additionally, in those patients with involvement of the soles of the feet, a greater concentration of DMF in the front part of the sole of the shoe was noted. In those cases where the DMF concentration was similar in the upper and the sole (samples 4 and 8), the patients had involvement of both the dorsa and the soles of the feet. One possible explanation for the location of the lesions is that DMF has different level of adherence to different materials, but there is no information in the literature regarding this.

In theory, given the volatility of DMF, its concentration in footwear should fall over time. However, DMF was present in a child's boot 1 year after it was taken out of the bag in the shoe box containing DMF, and, moreover, the concentration was still similar to that previously found in its pair 1 year beforehand (8). Thus, withdrawing the sachets with DMF may not be a sufficient preventative measure, as the footwear can remain impregnated with DMF for a long time. This preventative measure should, perhaps, be accompanied by suitable ventilation of the footwear. If the above is indeed the case, then we may continue seeing cases of dermatitis of the feet caused by DMF despite its prohibition, as many persons may have

kept these shoes and, even after some time, the DMF will remain and may again trigger severe contact dermatitis in previously sensitized patients.

Conclusions

The preferential sites of lesions in patients suffering from shoe-induced contact dermatitis caused by DMF are the dorsa of the feet and the dorsa of the toes. Correlations between the concentrations of DMF in the various parts of the footwear and the localizations of the lesions have been determined. Additionally, although DMF is a volatile substance, we found that footwear can remain impregnated for a long time after contact with the source of exposure and, accordingly, simply taking the DMF sachets out of the shoe boxes may be an inadequate preventative measure.

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