

Immunological contact urticaria caused by dimethyl fumarate

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doi:10.1111/cod.12230

Key words: dimethyl fumarate; gas chromatography; immunological contact urticaria; jeans; mass spectrometry.

Dimethyl fumarate (DMF) is a well-known contact irritant and sensitizer that has been responsible for severe contact dermatitis (1–3). Up to now, immediate hypersensitivity caused by DMF has never been reported.

Case Report

A 30-year-old non-atopic woman in good general health was referred for itchy contact urticaria (CU) on the internal surfaces of the lower limbs (Fig. 1). There was evident sparing of a linear area corresponding to the inside seam of her trousers. This immediate reaction appeared a few minutes after she started wearing a pair of skinny jeans, washed three times previously and bought from a Chinese bazaar. No respiratory or gastrointestinal tract signs were referred. CU resolved without residual signs 12 hr after the jeans had been removed and with the use of topical betamethasone. The patient reported two other episodes of CU on her lower limbs in the previous 2 weeks, occurring 30 min after she had worn the same jeans (brand name 'Miss bonbon').

Patch tests were performed with the Società Italiana di Dermatologia Allergologica, Professionale e Ambientale (SIDAPA) baseline series, a textile series (containing DMF 0.01% pet.), and dry and moistened pieces of the jeans. The allergens (FIRMA Diagent, Florence, Italy) were tested on the upper back with Haye's Test Chambers (Haye's

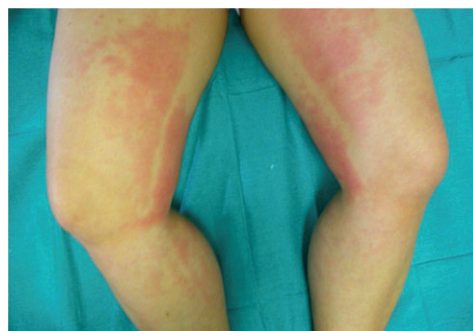


Fig. 1. Immediate contact urticaria on the lower limbs with a spared linear area corresponding to the inside seam of the trousers.

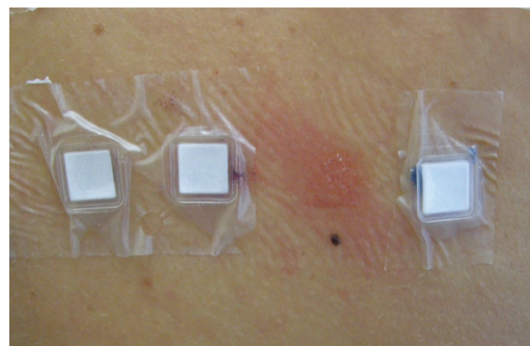


Fig. 2. Wheal and flare caused by dimethyl fumarate (0.01% pet.) at the 20-min patch test reading.

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Conflicts of interest: The authors declare no conflict of interests.

Service B.V., Alphen aan den Rijn, The Netherlands) on Soffix tape (Artsana, Grandate, Italy), and removed after 2 days. The readings (20 min, D2 and D4) were performed according to ICDRG criteria. At the 20-min patch test

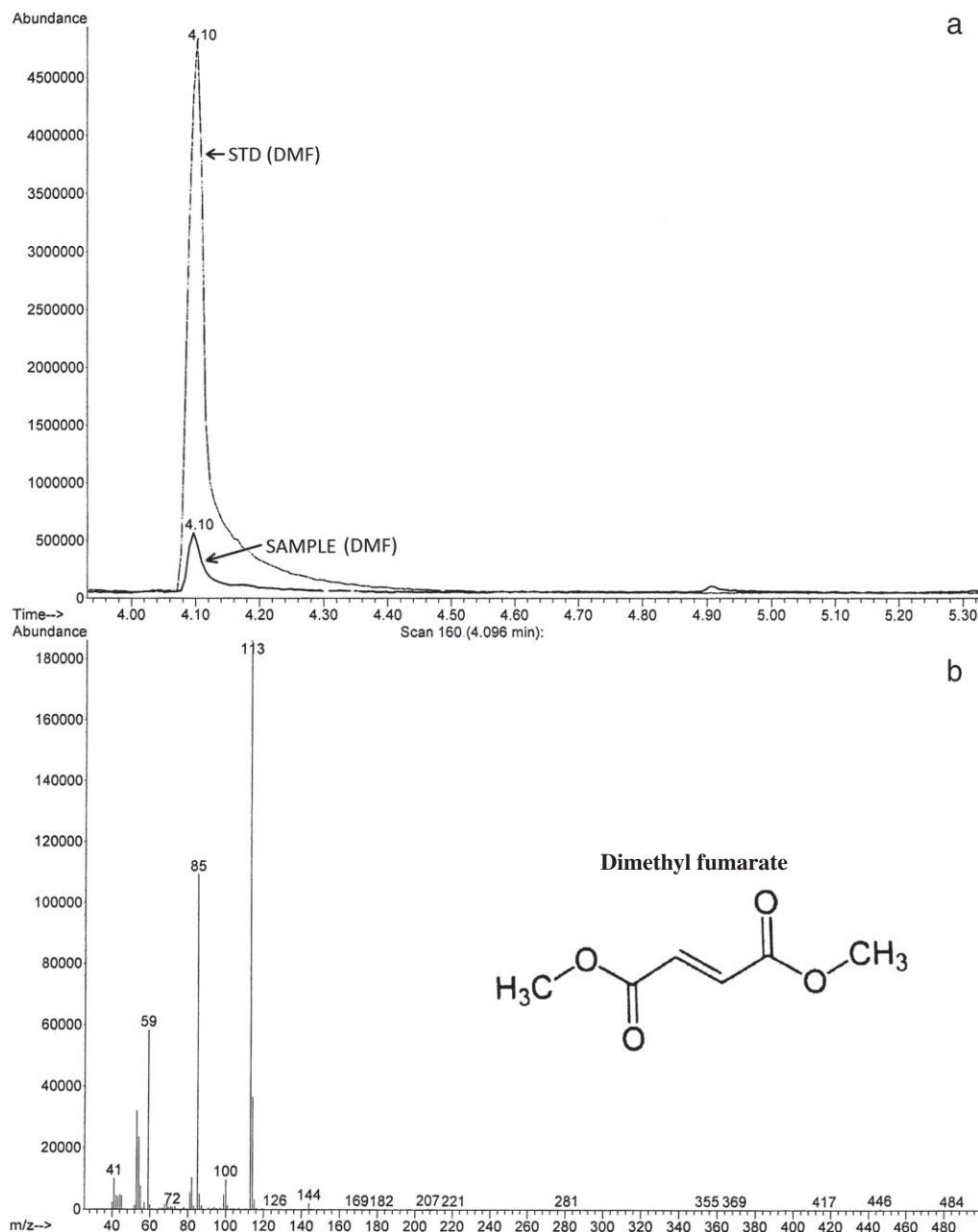


Fig. 3. (a) Gas chromatography–mass spectrometry chromatograms of samples taken from the patient's jeans (SAMPLE) and of a standard (STD) solution of dimethyl fumarate (DMF). (b) Mass spectrum (113, 114 and 85 m/z) of dimethyl fumarate (standard).

reading, a wheal and flare reaction to DMF was observed (Fig. 2); no positive reactions at the D2 and D4 readings were observed. To demonstrate immediate allergy to DMF, a prick test with DMF (0.01% in saline) was carried out on the volar aspect of the forearm. Control tests were performed with histamine (positive control) and normal saline (negative control). An immediate positive reaction was observed at 20 min (+++, >histamine). Prick

tests with DMF in 10 healthy volunteers gave negative results.

Chemical–toxicological analysis for the detection of DMF was performed by the Laboratory of Forensic Toxicology of the Institute of Legal Medicine, University of Perugia, Section of Terni.

We extracted the components of the jeans with two methods: acetone and methanol (4), and acetonitrile (5).

A concentration standard of DMF was prepared (0.2 mg/ml) and placed in acetone–methanol and acetonitrile. According to the method described by Davanzo et al. (4), we analysed four samples from the patient's jeans, $\sim 2 \text{ cm}^2$ each. Samples were cut from the inner side of the trouser leg (total net weight: 781 mg). They were fragmented into small pieces of $\sim 1 \text{ mm}^2$, and placed in 17 ml of acetonitrile. The sample and the standard of DMF were then extracted and sonicated in an ultrasonic warmed bath at 60°C for 30 min. Subsequently, acetonitrile was brought to dryness in a nitrogen stream at room temperature, and recovered with 200 μl of acetonitrile. The 60°C temperature was for greater efficiency of extraction, and a polar stationary phase such as the HP-5MS ensured good resolution of the chromatographic peak. The mass spectrum of DMF is very simple, and is characterized by very low masses. The molecular weight of DMF is 144.13 (g/mol). Identification was focused on the more characteristic masses: 85, 113 and 114 m/z (mass/charge ratio). As 113 m/z is the most representative, this can be used as the quantification ion.

One microlitre of standard DMF and sample were injected into a gas chromatograph coupled with a mass spectrometry (MS) instrument (Agilent Technologies 6890GC NetWork System 5973 Mass Selective Detector) (Agilent Technologies, Palo Alto, CA, USA).

The gas chromatography (GC) conditions were as follows:

Injector temperature: 290°C .

Inlet mode: splitless.

Capillary column: Hewlett-Packard (HP), 5 ms 325°C maximum, 15 metre (m) $\times$ $250 \mu\text{m}$ $\times$ $0.25 \mu\text{m}$ nominal.

Carrier (helium) flow rate: 1 ml/min.

Oven temperature program: setpoint 60°C (3 min) to 290°C (4 min).

The MS conditions were as follows.

MS: Electron Ionization (EI).

Electron energy: 70 eV.

Spectrum acquisition range: start at mass (amu) 40, end at mass (amu) 600.

Results

No traces of DMF in the acetone–methanol extract were found. In contrast, in the acetonitrile extract, the gas

chromatographic pattern of the internal samples was comparable to that of the DMF standard. Retention time (time of release of substance from column after injection) DMF = 4.10/min (Fig. 3).

Discussion

Delayed hypersensitivity to DMF is well known in the context of contact dermatitis (1–3). For this reason, EU Member States have banned the importation and marketing of products containing DMF used to inhibit mould growth in furniture, footwear and, more recently, clothes (6). Nevertheless, recent reports have highlighted the emergence of allergic contact dermatitis caused by DMF, which is a cheap and powerful antifungal agent commonly used by Chinese manufacturers to prevent contamination during the storage and transport of furniture (7). However, immediate CU caused by DMF is rare. White and Cronin reported a similar case caused by diethyl fumarate in a female university chemistry student (8). Among 17 cases of foot contact dermatitis caused by DMF, Giménez-Arnau described 2 children affected by itchy feet with immediate erythema and oedema a few hours after the first use of a new pair of leather boots (9). In these children, the diagnosis of non-immunological CU was supported by negative open and occluded patch test results with DMF. We underline that among IgE-mediated clothing CU cases this is the first one caused by DMF as shown by a positive immediate occluded patch test result and a positive prick test reaction with DMF.

It is interesting to note that only the extraction method with acetonitrile allowed us to show the presence of DMF in the jeans by GC/MS. Even though the jeans had been washed three times and GC/MS had been performed 6 months after the last washing, chemical analysis showed the presence of DMF. Despite the volatility of DMF, the jeans remained impregnated with DMF for a long time, as recently shown in footwear (10). Therefore, washing the jeans was an inadequate preventive measure.

Finally, it is surprising that CU spared a linear area on the inner side of the lower limbs corresponding to the inside seam of the jeans. External pressure caused by the thick seam was strong enough to inhibit the clinical appearance of CU at this site.

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