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Contact Dermatitis Due to Dimethyl Fumarate

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Abstract

Dimethyl fumarate is a fumaric acid ester. It has been used for some years to treat psoriasis and also as a preservative in desiccant sachets in the transport of furniture and footwear. Its irritant properties and sensitizing potential in contact with the skin were recently highlighted when it was implicated as the causative agent in 2 epidemics of severe acute eczema: sofa dermatitis in northern Europe and shoe dermatitis in Spain. The present article aims to guide dermatologists in the diagnosis and management of patients allergic to dimethyl fumarate. We review the clinical manifestations, results of patch tests, possible cross-reactions, and sources of exposure to dimethyl fumarate responsible for these skin reactions.

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Dermatitis de contacto por dimetilfumarato

Resumen

El dimetilfumarato es un éster del ácido fumárico que se utiliza desde hace años para el tratamiento de la psoriasis; además se emplea como conservante en bolsitas antihumedad para garantizar el transporte de muebles y calzado. Su capacidad irritante en contacto con la piel y su alta capacidad sensibilizante han quedado demostradas recientemente tras haber sido implicado como agente causal en dos epidemias de eccema agudo grave: por un lado, la «dermatitis del sofá» en el norte de Europa, y por otro lado, una epidemia de dermatitis por calzado en España. El presente artículo pretende orientar a los dermatólogos en el diagnóstico y tratamiento de los pacientes alérgicos al dimetilfumarato. Repasamos las manifestaciones clínicas, los resultados de las pruebas epicutáneas, las reacciones cruzadas existentes y las fuentes de exposición de dimetilfumarato que inducen estas dermatitis.

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Introduction

Dimethyl fumarate (DMF) has been used to treat psoriasis for many years.^{1,2} In Spain, however, the substance is little known and only rarely used by dermatologists. When physicians in northern Europe recently reported hundreds of cases of severe contact dermatitis caused by sofas and armchairs imported from China, DMF was identified as the causative agent.³⁻⁵ Very few cases of “sofa dermatitis” have been reported in Spain.⁶ However, since the summer of 2008 there has been a progressive increase in the number of cases of severe acute contact dermatitis caused by the presence of DMF in footwear. This epidemic has given rise to general alarm and has obliged the government to implement restrictive measures. The aim of the present article is to provide dermatologists with information on the diagnosis and treatment of patients with allergy to DMF.

Fumaric Acid and Its Esters: Uses and Applications

Fumaric acid is a white crystalline compound with the formula $C_4H_4O_4$. It is one of the two isomers of unsaturated dicarboxylic acid, the other being maleic acid. Fumaric acid is an endogenous intermediate compound in the citric acid cycle used by cells to produce energy in the form of adenosine triphosphate (ATP). It is also a product of the urea cycle. Human skin can produce fumaric acid naturally after exposure to sunlight.^{1,2} It is also found throughout the vegetable kingdom (the acid in fruit, for example) and is used as a food additive because of its acidulant properties. It is not considered toxic. Fumaric and maleic acids are both used in the plastics industry, especially in the manufacture of polyester resins and as a mordant for dyes.⁷

The salts and esters of fumaric acid are called fumarates. DMF, with the chemical formula $C_6H_8O_4$, is the methyl ester of fumaric acid and has been shown to be an effective bread mold inhibitor. It also has antibacterial activity against *Escherichia coli*.^{8,9} As a result, it is used in numerous products to prevent mold growth during sea transport. The fumaric acid esters are also used to treat psoriasis. Their antipsoriatic effect was discovered in 1959 by Schweckendiek,¹⁰ a German chemist who had psoriasis and developed the theory that fumaric acid deficiency could be a key factor in the pathogenesis of the disease. DMF, the most effective ester in this setting, is used alone or in combination with monoethyl fumarate, another fumaric acid ester. A blend of fumaric acid esters was registered in Germany and Holland in 1994 as an oral treatment for plaque psoriasis.^{1,11} This therapy is considered to be effective in 50% to 70% of cases, although serious side effects, such as its toxic effect on the kidney and lymphocytopenia have been reported.

Adverse Skin Reactions

Once the antipsoriatic efficacy of oral fumaric acid esters had been established, the usefulness of topical formulas with the same combination was investigated. However, topical treatment was quickly ruled out when it was found

that both DMF and monoethyl fumarate provoked itchy erythematous reactions at the site of application and, furthermore, were ineffective in controlling the disease.² Cases have also been reported of an itchy maculopapular rash appearing on the arms and faces of pharmacy technicians whose job involves filling oral capsules with these substances.¹² Fumaric acid esters can also cause contact urticaria. White¹³ reported such a case in a pharmacy student in contact with diethyl fumarate and interpreted it as an irritant reaction because application of the substance in 20 healthy controls gave rise to similar, although milder, symptoms. A subsequent experimental study demonstrated the appearance of nonimmunologic contact urticaria in both guinea pigs and healthy volunteers following application of diethyl fumarate.¹⁴ Another experimental study demonstrated that both monoethyl fumarate and DMF were cytotoxic, could cause contact urticaria, and had moderate sensitizing properties.¹⁵ DMF was found to be more irritant than monoethyl fumarate, an effect attributed to its greater liposolubility and therefore increased cell permeability. Probably the reason why DMF is better tolerated orally than topically is because when taken orally it is, to a large extent, metabolized to monomethyl fumarate, which appears to be the bioactive metabolite.¹

In short, until the occurrence of these outbreaks of sofa and shoe dermatitis caused by DMF, reports of adverse skin reactions to this substance in clinical practice had been rare and anecdotal, and most of the conclusions had been drawn from experimental studies.

Sofa Dermatitis

In October 2006, Finnish dermatologists reported that they had treated a number of severe cases of extensive eczema. The clinical presentation was painful dermatitis affecting the back, buttocks, and posterolateral arms and thighs. Oral treatment was required because the condition proved refractory to topical corticosteroids. Hospital admission was required in some cases. The differential diagnosis included a number of skin diseases, including drug reactions and even cutaneous lymphoma.⁶ Hundreds of similar cases were later reported in the United Kingdom, and a connection with leather sofas and armchairs imported from China was soon established. Many patients reported having bought a chair of this type a few weeks or even several months prior to developing the condition. The rash began in the areas of the body that came into contact with the sofa, even though most of the patients had been wearing clothes while sitting. Some patients reported an improvement in the condition when they went on holiday.³⁻⁶

Patients reacted strongly to patch tests with samples of the chair upholstery. Clinicians initially thought that the rash was contact eczema caused by acrylates because approximately 30% of the patients had positive reactions to at least 1 acrylate. Later, up to $470 \mu\text{g}\cdot\text{kg}^{-1}$ of DMF was found in the sofas, and the patients tested positive in patch tests prepared using 0.01% to 0.001% aqueous solutions of DMF. Thus, the condition was shown to be allergic contact dermatitis due to DMF.⁵ No prior cases of

allergic contact dermatitis related to DMF had ever been reported, although sensitization to fumaric acid had been described in workers in the plastics and polymer industry.¹⁶ DMF is used in the furniture industry in China during the finishing and packing of products. It was present in sachets placed inside the sofas to prevent the growth of mold during transport by sea. Body heat and sweat probably facilitate the release of DMF, thereby increasing exposure and inducing sensitization.⁵

Although these armchairs were also sold in Spain, only very few cases of sofa dermatitis have been reported in this country.⁶

Shoe Dermatitis

In September 2008, Dr Giménez-Arnau reported to dermatologists attending a meeting of GEIDAC, the Spanish contact dermatitis and allergy working group, that she had treated a case of acute contact eczema affecting the feet and that the patient had a positive patch test reaction to a sample of the suspected shoe. The presence of DMF had been detected in the shoe on chemical analysis with gas chromatography and mass spectrometry. Over the following months, the authors of the present article compiled data on more than 20 cases of contact eczema caused by DMF¹⁷ and reported the findings to the relevant health authorities. This led to the imposition of a series of restrictive measures on imported goods. The publication of the news in the lay press gave rise to considerable social alarm. A similar case was recently published in France.¹⁸

The clinical presentation is usually very severe, and patients tend to report to hospital emergency services. Shoe dermatitis affects both feet, taking the form of severe acute eczema perfectly reproducing the outline of the shoes responsible for the problem (Figure 1). The eruption is characterized by edema, vesicles, and blisters and has a severe negative impact on the epidermal barrier. This is accompanied by pruritus, pain, or a burning sensation. When the condition progresses, the lesion resembles a burn. Patients often bring snapshots or photocopies showing the initial clinical presentation (Figure 2).

Most of the patients relate onset with the purchase of a new pair of shoes and report that the problem started only hours after they first wore the shoes or on the following day. Some patients have had problems with several pairs of new shoes, and some have even reported problems with old shoes that have been stored in a shoebox over the winter. In our earliest cases, patients reported buying the shoes in street markets and shops run by people of Chinese origin, but we later encountered patients who had purchased their shoes in conventional shoe shops. Several commercial brands were involved, and some brands were involved in several cases. To date all our adult patients have been women.

The eczema is refractory to treatment if the cause is not identified. It can last for weeks even when the correct treatment is administered, and some patients report painful and sensitive skin even with minor friction for months after the eczema has been cured. Many will remain sensitized to this substance, and we believe that sensitization requires



Figure 1 Clinical presentation in adults. Severe acute contact dermatitis. Blistering on the dorsal surface of the toes of both feet affecting the entire area of skin that came in contact with the new shoes.



Figure 2 Most patients bring the suspected shoes along with photographs or photocopies showing the clinical presentation when they come to the clinic.

only a very short period of exposure; in many cases a single contact is enough.

In the 2 pediatric cases (a 9-year-old girl and a 17-month-old boy), the clinical picture was different. The children developed bilateral edema and very marked erythema duplicating the outline of the new shoes they had worn for the first time only hours earlier. In both cases, symptoms resolved within a few days with no residual desquamation, and we interpreted the reaction as contact urticaria/angioedema (Figure 3).

Patch tests should be performed to confirm diagnosis and to rule out other possible causes. The potential for active DMF sensitization is unknown but the risk may be far from negligible. In children, therefore, we should restrict the use of patch tests with this substance to cases in which there is a high suspicion of allergic contact dermatitis due to DMF.

DMF can be obtained in hospital pharmacies. The concentration used in patch tests should not exceed 0.1%, and the DMF can be diluted in an aqueous solution or, if possible, in petroleum jelly. The appropriate concentration range is 0.01% to 0.1%. Although all our cases were diagnosed with the 0.01% concentration, we know that the use of a 0.1% dilution of DMF in control patients has not caused irritant reactions or active sensitization. We use petroleum jelly as a vehicle because it ensures the stability of the allergen and does not provoke irritant reactions. A preparation of 0.01% DMF in petroleum jelly has recently become commercially available (Figure 4).



Figure 3 Clinical presentation in pediatric patients. Contact angioedema affecting both the sole and the dorsum of the foot and reflecting the outline of the footwear.



Figure 4 Patch tests showing positive results for both dimethyl fumarate and the other fumaric acid esters.

Some of the patients who presented acute contact eczema related to DMF exposure did not subsequently develop delayed hypersensitivity to DMF; patch tests in these cases were negative and we interpreted the reaction as toxic-irritant contact dermatitis caused by DMF. Patch tests were also negative in the pediatric patients and these cases were interpreted as nonimmunologic contact angioedema.

Patch tests with a piece of the suspected shoe should also be carried out, particularly on the area of the skin with the greatest number of lesions (Figure 5). It is not necessary to moisten the shoe with water, acetone, or other solvents. The test is not always positive in patients allergic to DMF since it depends on whether or not DMF is present in the shoe when the test is carried out. However, in some cases of toxic contact dermatitis caused by DMF patients do have irritant reactions to patches prepared with samples of the footwear. Tests with sachets of desiccant are not recommended because of the high risk of local irritant reactions.

In addition to the DMF patch, a standard battery of skin tests, a specific footwear panel, and an acrylate series should be administered. Like the patients who had sofa dermatitis, several of the DMF-allergic patients in our series were also sensitized to acrylates⁴ (Figure 6). The explanation for this is that DMF is chemically related to low molecular weight acrylates, such as methyl acrylate, methyl methacrylate, and ethyl acrylate.

We also tested some of these patients with allergy to DMF for allergy to diethyl fumarate, dimethyl maleate, and diethyl maleate. All had positive patch tests for diethyl fumarate and dimethyl maleate, and some also reacted to diethyl maleate, indicating a cross-reaction among the 4 fumaric acid esters (Figure 4). The repercussions of this finding could be important because the salts of maleic acid are used in the manufacture of certain drugs, including some very common medications, such as the antihistamines pheniramine maleate and chlorpheniramine maleate. They are also used in the manufacture of plastics, coatings, lubricant additives, glues, sealants, and agriculture chemicals; as preservatives in oils; and in the dyeing and finishing of wool, cotton, silk, etc.¹⁹⁻²²



Figure 5 Most patients had positive patch test results with samples of the suspected footwear.



Figure 6 Some patients with allergy to dimethyl fumarate show delayed hypersensitivity to acrylates.

Some of the shoes that caused dermatitis in our patients were analyzed using gas chromatography and mass spectrometry, and large quantities of DMF were detected in all the footwear tested. Surprisingly, although the children's shoes were among those that contained the highest concentration of DMF, the children did not become sensitized. This may be explained by the immaturity of the immune system of small children or by the rapid identification of the agent responsible for the reaction.

In most cases, we believe that DMF was initially added to the desiccant sachets placed in the shoe boxes to improve the conservation of the footwear during transport. DMF is a highly volatile substance which, at high temperatures, could impregnate all parts of the shoes stored in the box. If this is the case, and despite the ban on DMF in Europe, we may continue to see cases of DMF-related foot dermatitis because many people may have stored footwear from previous seasons in shoeboxes containing DMF-containing sachets. This has already happened in some of our patients. In 1 case, DMF was found in a structural component of the shoe, in a layer of paper located in the hardest portion. While we do not know the implications of this finding, it may be that DMF was also used during the manufacture of these shoes.

Once the diagnosis has been confirmed, the patient should avoid all contact with footwear that has been exposed to DMF even after the desiccant sachets have been removed. In theory, the DMF level decreases when the shoe is ventilated, but we know that even a small quantity of DMF can be enough to produce symptoms in allergic patients.

At the request of the Ministry of Health and Consumer Affairs, the epidemiology teams of each Spanish autonomous community are monitoring the appearance of new cases in order to determine the magnitude and severity of the problem in Spain. Since the case notification procedure

varies from one autonomous community to another, the best course of action for physicians is to contact the epidemiology section of the public health service when a case is diagnosed.

Conclusions

DMF has been used as a preservative in desiccant sachets placed inside furniture and footwear during transport. It has been identified as the cause of epidemics of sofa dermatitis in Finland and the United Kingdom and of shoe dermatitis in Spain. Both the irritant properties of this substance when it comes in contact with the skin and its high sensitizing potential have been demonstrated. Many of the patients who are allergic to DMF are also allergic to other fumaric acid derivatives, some of which are used in the manufacture of certain drugs. These cross-reactions could, in theory, have important repercussions, although the actual implications are at present unknown. Although this use of DMF has now been prohibited in the European Union,²³ we should be alert to the detection of new cases because the substance is very probably still present in many shoe boxes stored in homes. We therefore recommend that DMF be included in the panel of patch tests for footwear.

Conflicts of Interest

The authors declare no conflicts of interest.

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