

in water, to each constituent 4 h before testing. In prick testing with these oxidized constituents, a strongly positive reaction (+++, wheal diameter: 9x8 mm) was observed with PTD diluted at 1/128 at 20 min. If an antioxidant, sodium sulfite, 0.1% in water, was added to the mixture of PTD and H₂O₂, diluted at 1/128, a much weaker reaction (wheal diameter: 3x3 mm) was observed in prick testing. Ten healthy controls tested with the oxidized PTD had negative prick tests.

■ Immediate reactions to hair dyes are rare, and only one case of a severe systemic reaction with shock, similar to ours, has been reported (5). In this case, the responsible molecule was an oxidation product of PPD. The mechanism by which PTD induces these reactions is not clearly understood. The reaction happens only when the PTD is oxidized by H₂O₂, and it is partially reversed when an antioxidant, sodium sulfite, is added to the mix. One can assume that the allergen involved is related to an oxidation product of PTD. With the help of the manufacturer, Goldberg et al. (5) were able to identify which oxidation product of PPD was causing the reaction. It was due to *N,N'*-bis-(4-aminophenyl)-2,5-diamino-1,4-quinone-diimine, known as Brandowski's base. A prick test with Brandowski's base was positive. In their case, due to unsuccessful RAST assay, specific IgE was not demonstrable. PTD and PPD are closely related compounds, and their oxidation products are chemically close. An analog of Brandowski's base could also constitute the hapten in our case, and/or another oxidation product of PTD. However, it was not possible to prick-test with Brandowski's base or any other oxidation product. Moreover, these oxidation products are unstable and short-lived.

In conclusion, this is the first case of recurrent extensive contact urticaria with systemic symptoms and shock due to an oxidation product of PTD. Immediate reactions to hair-dye constituents, although rare, may be life-threatening and should be known to the allergologist and the dermatologist.

Key words: contact urticaria; hair dye; paratoluenediamine; shock.

F. PASCHE-KOO*, L. FRENCH, P.-A. PILETTA-ZANIN, C. HAUSER

*Department of Dermatology of Western Switzerland
Geneva University Hospital
1211 Geneva 14
Switzerland

Accepted for publication 1 April 1998

Copyright © Munksgaard 1998

ALLERGY 1998;53:904-905

REFERENCES

1. De Groot AC, White IR. Cosmetics and skin care products. In: Rycroft RJG, Menné T, Frosch PJ, Benezra C. Textbook of contact dermatitis. Berlin: Springer-Verlag, 1992:467-8.

2. Edwards EK Jr, Edwards EK. Contact urticaria and allergic contact dermatitis caused by paraphenylenediamine. *Cutis* 1984;34:877.
3. Frosch PJ, Burrows D, Camarasa JG, et al. Allergic reactions to a hairdressers' series: results from 9 European centers. *Contact Dermatitis* 1993;28:180-3.
4. Guerra L, Bardazzi F. Contact dermatitis in hairdresser's clients. *Contact Dermatitis* 1992;26:108-11.
5. Goldberg BJ, Herman FF, Hirata I. Systemic anaphylaxis due to an oxidation product of *p*-phenylenediamine in a hair dye. *Ann Allergy* 1987;58:205-8.
6. Majoie IM, Bruynzeel DP. Occupational immediate-type hypersensitivity to henna in a hairdresser. *Am J Contact Dermatitis* 1996;7:38-40.
7. Wigger-Alberti W, Elsner P, Wüthrich B. Immediate-type allergy to the hair dye Basic Blue 99 in a hairdresser. *Allergy* 1996;51:64-5.

Anaphylactic shock due to fosfomycin

FOSFOMYCIN (FOM), or (-)-cis-1,2-epoxy-propylphosphonic acid, is a bactericidal antimicrobial belonging to the phosphonic acid antibiotics, whose spectrum of activity embraces all the common causes of uncomplicated urinary tract infection, and which are chemically unrelated to any other known antimicrobial agents. FOM is a well-tolerated drug and does not appear to cause serious reactions. Most reactions are gastrointestinal. There are no previous medical reports of allergic reactions to FOM; therefore, this drug is used as an alternative, especially when there are intolerance or allergic reactions to other antibiotics. Thus, previous studies have demonstrated an immunomodulatory effect caused by FOM. In fact, FOM can inhibit histamine release. This report describes the evaluation of a patient with no previous reaction to drugs who developed an anaphylactic reaction after taking FOM.

A 56-year-old woman, without personal or family history of atopy, undergoing treatment with tricyclic drugs for a depressive disorder, was prescribed FOM for a urinary infection. After a therapeutically recommended dose, she presented an immediate systemic reaction including vomiting, diarrhea, flushing, generalized itch with urticaria, dyspnea, wheezing, and dizziness. She did not lose consciousness. The patient was not taking any other drug apart from FOM. She required treatment in an emergency room. Subcutaneous epinephrine, intravenous saline, and corticosteroids were administered. Clinical examination revealed hypotension, generalized rash, wheezing, and hypoxemia. Complementary studies (hemogram, biochemical parameters) demonstrated no alteration. Anaphylactic shock was diagnosed. The patient could not

remember whether she had been previously treated with FOM or not. Since then, the patient has tolerated other antibiotics of various groups such as β -lactams and aminoglycosides. She has continued taking tricyclic drugs without reaction.

A battery of commercially available common inhalants (Abelló, Madrid, Spain) was used to perform skin prick tests. Commercial preparations of FOM were used for *in vivo* and *in vitro* tests at a concentration of 10 mg/ml, diluted in phosphate-buffered saline (PBS), pH 7.3. An anaphylaxis protocol was also performed including latex (Leti, Barcelona, Spain) and *Anisakis* (IPI, Madrid, Spain) antigens. Cutaneous sensitivity to FOM was evaluated by skin prick test and intradermal test. Histamine acid phosphate and 0.9% normal saline were used as positive and negative cutaneous test controls, respectively. The reaction was observed after 15 min by measuring the widest diameter of the wheal. In the skin prick test, a wheal of at least 3 mm larger than the negative control was considered positive. Ten atopic and 10 normal subjects served as controls. Total serum IgE and latex- and *Anisakis*-specific IgE were determined by the CAP technique, according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden). The histamine-release test was performed by an automated fluorometric method (1) subsequently modified (2). A result higher than 10% release was considered positive.

The results of the skin prick test with a commercial battery of common allergens were negative, as were the anaphylaxis protocol test, including the latex and *Anisakis* prick tests. Skin prick test with FOM elicited a positive reaction of 6-mm wheal diameter. An intradermal test resulted in a wheal size of 17 mm (positive control was 10 mm). However, these tests were negative in atopic and normal control subjects. Latex- and *Anisakis*-specific IgE was negative, and the blood total IgE level was normal. The histamine-release test was not conclusive because it showed a low level of release. The oral challenge test was not performed because of the anaphylactic clinic.

We report the first case of anaphylaxis caused by FOM, and we demonstrate that apparently safe drugs such as FOM, generally well tolerated, can cause allergic reactions. The appearance of im-

mediate symptoms after administration of FOM suggested the diagnosis, and the positive cutaneous tests with FOM (10 mg/ml) had high diagnostic value. Therefore, these observations suggest an IgE-mediated mechanism. The negative histamine-release test may have several explanations. In the first place, this patient had been treated with other drugs that possibly inhibit histamine release, such as tricyclic drugs. And on the other hand, previous studies (3) have shown that FOM may have an immunomodulatory effect. This drug can suppress histamine release *in vitro* from blood basophils by a dose-dependent mechanism, although most clinically used antibiotics do not have the immunomodulatory capacity to release histamine directly from human basophils or to inhibit histamine release. Bertelli et al. (4) have demonstrated that FOM can elevate cyclic AMP levels from rat peritoneal mast cells, with subsequent inhibition of cell degranulation. Recent reports (5) have examined the effect of FOM on human B-cell functions and have demonstrated that FOM inhibits the proliferative response of resting B cells to *Staphylococcus aureus* Cowan 1 in a dose-dependent manner. In fact, FOM interferes with the transition from the G_0 to the G_1 phase in the cell cycle, leading to cell arrest, and, in addition to this, it suppresses immunoglobulin secretion by antibody-producing B cells. However, the mechanism of the effect of FOM on either IgE- or non-IgE-mediated histamine release has not been fully clarified.

This immunomodulatory effect suggests that FOM can be considered and used advantageously in the treatment of certain bacterial infections in patients with autoimmune and chronic inflammatory disorders including bronchial asthma (6). In fact, FOM is used clinically in combination with steroids to reduce the dose of steroids for patients with severe bronchial asthma. It is unknown whether FOM may compensate for the immunoregulatory action of steroids.

In summary, this patient expressed remarkable specificity of hypersensitivity, reacting to FOM without reaction to other drugs. In any case, in view of the lack of reports of FOM hypersensitivity despite the widespread use of this drug, especially when there are allergic reactions to or intolerance of other antimicrobials, one may assume that its allergenic potential is low. This fact can be explained by its immunomodulatory effect, capable of interfering with the allergic reactions. We wish to emphasize that well-tolerated drugs such as FOM may be a potential cause of anaphylactic shock in susceptible subjects.

Key words: adverse reaction; anaphylaxis; antimicrobial; fosfomycin; hypersensitivity; immunomodulatory effect.

*Well-tolerated and
apparently safe drugs
such as fosfomycin
may cause
anaphylactic shock in
susceptible subjects.*

M. J. ROSALES*, F. VEGA

*Allergy Section

Hospital de la Princesa

C/ Diego de Leon. N° 62

28006 Madrid

Spain

Tel. 34-1-520 22 39

Fax: 34-1-401 35 82

Accepted for publication 29 May 1998

Copyright © Munksgaard 1998

ALLERGY 1998;53:905-907

REFERENCES

1. Siraganian RP. An automated continuous flow system for the extraction and fluorometric analysis of histamine. *Ann Biochem* 1974;57:383-94.
2. Moneo I, Bootello H, Hinojosa M, Alcover R. Nuevos avances en la determinación de histamina automatizada. *Allergol Immunopathol (Madr)* 1980;Suppl 7:311-15.
3. Ida S, Shindoh Y, Takishima T. Effect of antibiotics on immediate hypersensitivity reactions *in vitro*: suppression of IgE-mediated histamine from peripheral blood basophils by fosfomycin. *Microbiol Immunol* 1987;31:975-84.
4. Bertelli A, Schinetti ML, Greco R. Protective effects of fosfomycin against experimentally induced mast cell degranulation. *Minerva Med* 1978;69:4071-3.
5. Morikawa K, Oseko F, Morikawa S. Immunomodulatory effect of fosfomycin on human B-lymphocyte function. *Antimicrob Agents Chemother* 1993;37:270-5.
6. Mue T, Otsu H, Taniguchi Y, et al. Antibiotic therapy of bronchial asthma - a clinical effect of fosfomycin administration. *Prog Med* 1993;3:1582-8.

Occupational asthma caused by sunflower-seed dust

SUNFLOWER (*Helianthus annuus*) belongs to the Botanic family of Compositae. Sunflower seeds are widely used in the production of margarine and cooking and salad oils, as well as livestock, bird, and poultry food. Anaphylactic reactions have been reported after ingestion of sunflower seeds (1, 2), sunflower oil (3), and honey containing sunflower pollen (4). Rhinitis and asthma have been documented in workers exposed to sunflower pollen (5, 6) and in people living in sunflower-growing areas (6). We herein present the case of a baker who developed rhinitis and asthmatic reactions when exposed to sunflower-seed dust at work.

A 31-year-old man had been working as a baker between 1981 and 1990 without experiencing respiratory symptoms. He had smoked 25 cigarettes a day since the age of 15 and reported a history of mild and transient asthma during childhood. In 1990, he was hired to work in a bakery where various "natural health" breads were produced, including bread flavored with sunflower seeds. About 3 months later, he developed rhinoconjunctivitis and asthma when exposed to dried sun-

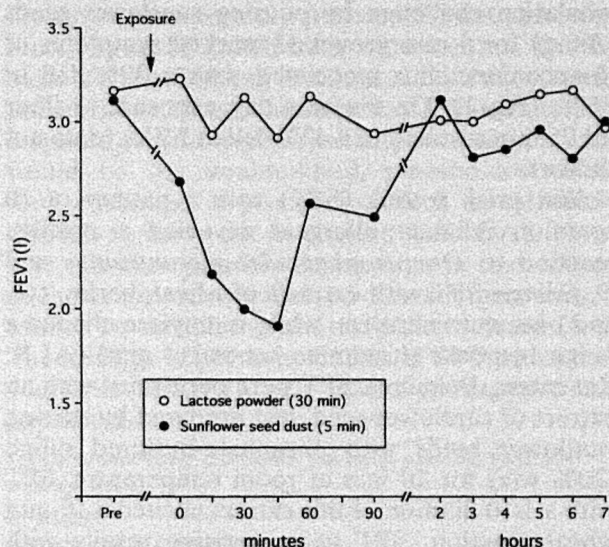


FIGURE 1 Results of inhalation challenges showing changes in FEV₁ after exposure to lactose powder for 30 min (open circles) and to sunflower-seed dust for 5 min (closed circles).

flower seeds, even when the seeds were handled only by his coworkers. The subject reported having experienced an anaphylactic reaction after eating about half a sunflower seed. He noticed that his respiratory symptoms worsened progressively and became less specifically related to exposure to sunflower seeds. In February 1995, the subject decided to work in another bakery where he was no longer exposed to sunflower seeds. He still experienced rhinitis and asthma at work, as well as nocturnal asthma attacks. In April 1996, he had to stop working, because he was experiencing severe asthma symptoms despite treatment with inhaled fluticasone propionate and salbutamol.

A baker developed rhinitis and asthma after workplace exposure to sunflower-seed dust.

Inhalation challenge tests were carried out in the laboratory 8 months after avoidance of workplace exposure. Baseline lung function testing showed an FEV₁ of 3.17 l (72% predicted value) with an FEV₁/forced vital capacity ratio of 62%. As a control challenge, the subject tipped lactose powder from one tray to another for 30 min without eliciting significant changes in FEV₁ (Fig. 1). At the end of this control day, the provocative concentration of histamine causing a 20% fall in FEV₁ was 0.18 mg/ml, reflecting marked nonspecific bronchial hyperresponsiveness. On the next morning,

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.