Fixed Drug Eruption Due to Dextromethorphan With Tolerance to Other Opioids

G Davila-Fernández, S Vázquez-Cortés, MJ Moreno-De Vega, M Chamorro-Gómez, A Elices-Apellániz
1 Hospital Universitario del Henares, Department of Allergy, Madrid, Spain
2 Hospital Universitario del Henares, Department of Dermatology, Madrid, Spain

Key words: Cross-reactivity. Dextromethorphan. Fixed drug eruption. Opioids. Patch test.

Dextromethorphan is a synthetic morphine derivative used as a cough suppressant in the form of hydrobromide salt. It is widely used, either alone or in combination with other compounds, but there have been few published reports of adverse cutaneous reactions.

Only 2 cases of fixed drug eruption (FDE) due to dextromethorphan have been reported in the literature [1,2] and neither of them evaluated possible cross-reactivity with other opioids.

A 63-year-old man, with no history of atopy, started treatment with a combination drug (dextromethorphan 15 mg + acetaminophen 500 mg) for a common cold (1 capsule every 8 hours). On the third day of treatment, he developed a round, erythematous, well-circumscribed plaque of 2 cm in diameter on the right cheek. The plaque disappeared spontaneously in 8 days, leaving residual hyperpigmentation. The patient had previously tolerated both drugs.

Two months after the reaction, patch tests were performed with dextromethorphan and with acetaminophen 10% in petrolatum [1-3] on normal and involved skin, with negative results.

After another 2 months, a single-blind placebo-controlled oral challenge test with dextromethorphan was performed after obtaining the patient’s written consent. Ten hours after drug intake, the patient developed the same erythematous plaque of 2 cm in diameter on the right cheek.

A single-blind placebo-controlled oral challenge test with acetaminophen was well tolerated.

To evaluate possible cross-reactivity, single-blind oral challenge tests with meperidine, morphine, fentanyl, codeine, and tramadol were also performed, with good tolerance.

FDE is a common adverse drug reaction, characterized by the sudden onset of single or multiple, round, edematous, erythematous-violaceous plaques. These reactions normally resolve with residual hyperpigmentation [1-3]. The most characteristic finding of FDE is recurrence of similar lesions at the same site with reexposure to the drug [1-4], as occurred in the present case.

A variety of drugs have been found to cause FDE [1-4]. Although dextromethorphan is one of the most widely used cough suppressants, only 2 cases of dextromethorphan-related FDE have been reported to date [1,2].

Patch tests are useful in a significant number of patients and have been recommended as the initial diagnostic tool in FDE [3,4]. However, when patch tests are negative, systemic drug reexposure is necessary to confirm the diagnosis.

Patch testing at the site of a previous lesion yields a positive response in up to 43% of cases of FDE [5]. Reactivity depends on the drug and the vehicle, is usually seen within 24 hours, and is observed exclusively on lesional skin.

Patch tests performed in the 2 previously reported cases of FDE due to dextromethorphan were negative [1,2], possibly due to insufficient penetration of the drug or to the fact that the FDE was caused by a derivative of dextromethorphan rather than the compound itself [1,2].

Dextromethorphan is the methylated dextrorotatory analog of levorphanol, which is a phenanthrene derivative, like codeine and morphine. On the basis of similarities in

Figure. Phenanthrene derivatives
chemical structure (Figure), the safest approach in patients sensitized to dextromethorphan would be avoidance of all chemically related opioids [6,7]. In the present case of FDE due to dextromethorphan, we have demonstrated no cross-reactivity with morphine, codeine, or other opioids, including meperidine, fentanyl, and tramadol. These opioids could be a safe alternative in patients with FDE to dextromethorphan.

References


Allergic contact dermatitis is an eczematous skin disease caused by cell-mediated hypersensitivity after skin contact with an allergen to which the patient has developed a specific sensitivity, such as a topically applied drug. In a study where patients with suspected drug allergic contact dermatitis were tested with epicutaneous patch tests, the most frequent drugs implicated in the reactions were neomycin sulfate, bufexamac, bacitracin, gentamicin sulfate, framycetin sulfate, polymyxin B sulfate, amcinonide, and hydrocortisone-17-butyrate [1]. Allergic reactions to rifamycin are uncommon and there are few reports in the literature of severe anaphylactic reactions after the topical use of rifamycin SV [2,3]. There have also been few reports of contact urticaria [4] and delayed reactions [5-8]. Rifamycin SV is a semisynthetic antibiotic belonging to the class of ansamycins obtained from rifamycin B, which is produced by fermentation of Streptomyces mediterranei. The drug is used topically to treat infected wounds and prevent local sepsis as it has a broad spectrum of activity against gram-positive and some gram-negative bacteria.

A 70-year-old man without any personal or family history of atopy developed pneumonia and empyema. Thoracic radiography showed pleural effusion in the left hemithorax, which led to the patient being admitted to hospital for open thoracostomy drainage. After surgery, he was treated with topical rifamycin solution twice daily for 2 months. At an outpatient follow-up visit, the patient complained of itching erythema at the site of application (Figure A). The drug was discontinued and the patient was advised to replace it with saline solution. The reaction disappeared after discontinuation of the drug. A patch test with 1%, 10%, and 30% pure rifamycin (Sigma-Aldrich) in petrolatum was performed after obtaining the patient’s written consent. On examination after 72 hours, the test revealed erythema and slight infiltration (+). Seven days later, erythema, infiltration, and vesicles (++) were observed at the application site (Figure B). Patch test reading...
on day 7 is suggested for certain drugs named late reactors, such as neomycin and corticosteroids [9]. Based on our observations, rifamycin might also be considered a late reactor. The epicutaneous patch test with rifamycin was also performed in 10 healthy volunteers with no history of drug allergy, and negative results were obtained in all cases.

We have reported a case of delayed hypersensitivity reaction mediated by T cells after the topical application of rifamycin. The clinical data and positive patch testing confirmed the diagnosis of drug allergic contact dermatitis. The assessment criteria for determining the probability of adverse drug reactions established by the Uppsala Monitoring Centre (UMC)/WHO Collaborating Centre for International Drug Monitoring [10] indicated a definitive causality between rifamycin and the development of allergic contact dermatitis in our patient.

Contact dermatitis due to topically applied drugs may be caused by allergy to not only the agent but also its constituents, such as preservatives or excipients. Milpied et al [6] reported 2 cases of allergy, one involving a patient sensitized to rifamycin and the other involving a patient allergic to potassium metabisulfite; both cases were confirmed by epicutaneous tests. The patients had a background history of atopy and the authors considered this condition to be a risk factor for drug hypersensitivity. In the present case, the epicutaneous test was performed using the pure form of rifamycin in order to confirm that the clinical manifestations were related to the drug and not the excipients.

Balato et al [7] described the case of a 30-year-old woman without a history of atopy who developed allergic contact dermatitis after the topical use of rifamycin on a leg ulcer. The patch test with 0.5% rifamycin in petrolatum was positive. Guerra et al [8] reported 3 cases of allergic contact dermatitis in adult patients after the topical application of rifamycin on a leg ulcer (2 patients) and post-surgical wounds (1 patient). The skin lesions had late onset and disappeared gradually after the drug was discontinued. One patient presented clinical manifestations similar to those seen in our case, namely, erythema, itching, and edema around the wound after 2 months of treatment. The patch tests with 2.5% rifamycin in petrolatum were positive in all cases.

In conclusion, although neomycin is the most common allergen in topical antibacterial preparations, rifamycin topically applied to the skin should also be considered a potential causative agent of adverse drug reactions, ranging from mild reactions such as allergic contact dermatitis to potentially life-threatening anaphylaxis.

**Funding**

This study was financially supported by the CNPq (process 554970/2010-4) and FUNCAP/CAPES (process BMD – 1401-2.08/08).

**References**


*Manuscript received October 4, 2012; accepted for publication, November 20, 2012.*

**Fabricia Martins Teixeira**

Dept. of Clinical Analysis and Toxicology  
Faculty of Pharmacy  
Universidade Federal do Ceará  
Rua Capitao Francisco Pedro, 1210  
CEP 60430-370 Fortaleza, Ceará, Brazil  
E-mail: briciamt@yahoo.com.br
Changes in the Asthma Control Test Score in Patients With Work-related Asthma

S Quirce,1 X Muñoz,2,3 I Urrutia,4 I Pérez-Camo, C Sabadell, J Domínguez-Ortega, P Barranco, V Plaza
1 Department of Allergy, Hospital La Paz Institute for Health Research (IdiPaz), Madrid, Spain
2 CIBER de Enfermedades Respiratorias (CIBERES), Institute Carlos III, Ministry of Health, Madrid, Spain
3 Department of Pneumology, Hospital Vall d’Hebron, Barcelona, Spain
4 Department of Pneumology, Hospital de Getafe, Getafe, Spain
5 Department of Pneumology, Hospital de Galdakao-Usansolo, Bizkaia, Spain
6 Allergy Consultant, Mutua MAZ, Zaragoza, Spain
7 Department of Pneumology, Hospital de Figueres, Girona, Spain
8 Department of Allergy, Hospital de Getafe, Getafe, Spain

Key words: Occupational asthma. Asthma Control Test. Work-related asthma.

Occupational exposures can induce or exacerbate asthma, leading to work-related asthma (WRA), which is estimated to affect as many as 25% of adult asthmatic patients [1]. WRA comprises 2 major entities: occupational asthma (OA), defined as a type of asthma caused by workplace exposures, and work-exacerbated asthma (WEA), which refers to the worsening of asthma triggered by various work-related factors (eg, irritants, aeroallergens, and exercise) in workers who are known to have preexisting or concurrent asthma [1].

Whereas the diagnostic approach in OA has been extensively appraised [1], few studies address the clinical evaluation and diagnosis of WEA. According to the American Thoracic Society statement on WEA [2], diagnosis requires the demonstration of a relationship between work exposure and asthma exacerbation. This relationship is most commonly documented by recording changes in symptoms (frequency and severity) or medication use temporally related to work [2], which in turn imply changes in asthma control.

In this study we aimed to measure the variability of asthma control during periods at work and away from work in patients with WRA. Asthma control was assessed using a validated tool, the Asthma Control Test (ACT). The ACT is a self-completed questionnaire on asthma control comprising 5 questions that assess activity limitation, shortness of breath, nighttime symptoms, use of rescue medication, and patient rating of asthma control over the previous 4 weeks [3]. The questions are scored from 1 (worst) to 5 (best), and the ACT score is the sum of the responses, with a maximum best score of 25. A score of ≥20 is the optimal cutoff point defining well-controlled asthma over the previous 4 weeks [3,4]. In a population of Spanish asthma patients, the optimal cutoff points for the asthma control levels defined by the Global Initiative for Asthma (GINA) would be an ACT score of >20 for controlled asthma, 19–20 for partly controlled asthma, and ≤18 for uncontrolled asthma [4]. This study population included patients older than 18 years who had been diagnosed with WRA in the allergology department (n=3) or pneumology department (n=3) at 6 hospitals in Spain.

The design of the study was prospective, with study periods of up to 4 weeks at work and 4 weeks away from work. Asthma was defined according to the GINA criteria. OA was defined as the worsening of asthma symptoms in the workplace with a positive specific inhalation challenge (either in the laboratory or at the workplace); WEA was defined as the worsening of asthma symptoms in the workplace with a negative specific inhalation challenge. The patients were seen while they were working (for at least 4 weeks) and again after 4 weeks away from work. On the first occasion, patient characteristics were documented and spirometry and a methacholine challenge test were performed. At both visits, asthma control was evaluated using the ACT questionnaire. Patients were asked not to change their asthma maintenance treatment during the study period, but they were free to use short-acting β2-agonists as needed.

We used descriptive statistics to analyze demographic data. Results were expressed as mean (SD), except for the provocative concentration of methacholine inducing a 20% fall (PC_{20}) in the forced expiratory volume in 1 second (FEV1), which was expressed as the geometric mean with minimum and maximum values. Within-group differences in the outcome measure (ACT score) between periods of exposure (at work) and nonexposure (off work) were analyzed using a paired t test. A 2-tailed unpaired t test was used to compare the different variables between the 2 groups.

The study sample comprised 47 patients with WRA (33 with OA and 14 with WEA). Among the patients with OA, 20 were sensitized to high-molecular-weight agents (cereal flour or baking additives, 15; wood dust, 3; animal dander, 1; Plantago ovata, 1), and 13 to low-molecular-weight agents (diisocyanates, 7; amines, 3; styrene, 1; acrylates, 1; persulfate, 1), and patients with WEA were all exposed to low-molecular-weight agents (cleaning products, 5; diisocyanates, 3; copier toner, 2; persulfate, 1). No differences in baseline characteristics were detected between the 2 groups for age, duration of symptoms, atopy, smoking status, lung function, or bronchial hyperresponsiveness to methacholine (Table). Patients with OA had worse asthma control at work than patients with WEA, as shown by lower (but not significantly so) ACT scores. Moreover, according to the GINA severity classification, patients with OA had more severe disease than patients with WEA. All patients in both groups had suboptimally controlled asthma while at work. Both groups showed a statistically significant increase in their ACT score after a work absence of 4 weeks, as compared with the ACT score at work (Table). The differences in the ACT score off work between the 2 groups were not significant.

Patients with WEA and persistent work-related symptoms have clinical characteristics (level of severity, medication needs) and adverse socioeconomic outcomes (unemployment, reduction in income) similar to those of patients with OA [2,5].
The level of bronchial hyperresponsiveness was also similar in both conditions [6]. In the USA, the frequency of emergency room visits and hospitalizations for asthma was shown to be similar in both WEA and OA [7].

WEA has been diagnosed most commonly by self-report of worse asthma symptoms on the job in workers with preexisting asthma [2]. However, a definitive diagnosis of WEA should be based on objective indicators of worsening of asthma related to the work environment [8]. The worsening of asthma symptoms at work and serial peak expiratory flow rate monitoring [9] do not enable us to differentiate OA from WEA. Induced sputum may provide more information, as an increase in eosinophil counts at the workplace suggests OA [10]; however, this test requires technical expertise and is not routinely available.

According to our results, a validated questionnaire such as ACT could be a useful and objective tool to document work-related changes in asthma control in the diagnosis of WEA; in addition, it could play an important role in the diagnostic workup of OA. However, the ACT score does not enable us to differentiate between the 2 types of WRA.

Funding

No financial support was received for this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


Manuscript received October 29, 2012; accepted for publication November 27, 2012.

Santiago Quirce
Servicio de Alergia
Hospital La Paz
P. La Castellana 261
28046 Madrid
E-mail: squirce.hulp@salud.madrid.org

Occupational Contact Dermatitis to Methacrylates in an Orthopaedic Operating Room Nurse

V Ponce, F Muñoz-Bellido, A González, M Gracia, A Moreno, E Macías
Hospital Universitario de Salamanca, Salamanca, Spain

Key words: Methacrylates. Occupational. Contact dermatitis.

Contact dermatitis accounts for about 95% of all occupational skin diseases and is due mainly to irritant mechanisms; 80% of all cases of contact dermatitis affect the hands [1]. We report a case of occupational allergic dermatitis involving the hands of an operating room nurse who handled bone cement used mainly for knee replacements.

A 40-year-old man was referred to our department for evaluation. For 6 months, he had presented erythema, edema, blistering, and subsequent cracking on the fingertips and sides of the second, third, and fourth fingers of the right hand and the fourth finger of the left hand. He had previously been diagnosed by the dermatology department with contact sensitization to thiomersal and mercury chloride.

Given the persistence of the lesions, their location, and the occupational exposure of the patient to bone cement (Palamed®, Heraeus), which contained poly-(methyl acrylate, methyl methacrylate), zirconium dioxide, benzoyl peroxide, colorant E 141, mono methyl methacrylate, N, N-dimethyl-p-toluidine, and hydroquinone, we performed patch tests with a series of bone cement components and other prosthesis components not previously tested.

Patch tests were performed with methyl methacrylate 2% in petrolatum (pet) (MMA), triethylene glycol dimethacrylate 2% pet (TEGDMA), ethylene glycol dimethacrylate 2% pet, hydroxyethyl methacrylate 1% pet (HEMA), benzoyl peroxide 1% pet, N,N-dimethyl-p-toluidine 5% pet, hydroquinone monobenzyl ether 1% pet, 2-hydroxy-4-methoxy benzophenone 2% pet, titanium oxide 5 % pet, palladium-A dimethacrylate 2% pet, and vanadium 1% pet (allergen occlusion for 2 days with Curatest and Hypo tape, Lohmann and Rausher International). An erythematous papular reaction was observed at days 2 and 4 with MMA, TEGDMA, and HEMA (Figure).

Further, mass production of surgical gloves might result in imperfections, with areas of low material thickness or even small holes, which would allow the rapid penetration of monomers [5].

Our patient was advised to change his workplace. However, he decided to stay in the orthopedic operating room but to avoid handling bone cements. When he has occasionally had minimum contact with bone cement, he has developed mild erythema, itching, and small vesicles on his fingertips in the space of minutes or a few hours, despite using double rubber or nitrile gloves.

References


Manuscript received September 6, 2012; accepted for publication, December 5, 2012.

Vanessa Ponce
Paseo San Vicente 58-182
37007 Salamanca, Spain
E-mail: lvpg77@gmail.com

© 2013 Esmon Publicidad

J Investig Allergol Clin Immunol 2013; Vol. 23(4): 281-288
Wheat allergy can be expressed in different immunoglobulin (Ig) E-mediated clinical phenotypes (baker’s asthma, food allergy, or wheat-dependent exercise-induced anaphylaxis). Protein contact dermatitis has also been observed, albeit less frequently [1,2]. Avoidance of wheat is the first step, although this may not always be feasible in occupational settings. Immunomodulatory therapies such as wheat-specific immunotherapy and anti-IgE monoclonal antibodies (omalizumab) are other available options.

We describe the case of a 38-year-old male baker diagnosed 8 years ago with wheat-induced rhinoconjunctivitis and asthma. Wheat immunotherapy for 5 years resulted in the resolution of his respiratory symptoms.

Six years ago, he developed eczematous lesions on the dorsum of both hands, which, 3 years later, expanded to the antecubital and retropopliteal areas, groin, neck, and arms. The patient’s symptoms were related only to wheat flour as he worked exclusively with this kind of flour. A 4-fold increase in nonsedative antihistamines for 4 weeks produced no response and neither did adding montelukast and H2-antihistamines. Nonsedative antihistamines for 4 weeks produced no response. The patient’s symptoms were related only to wheat flour.

Patch tests with the standard series of the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) and with the wheat flour used by the patient were negative. Prick tests with a series of common inhalants and food allergens were positive for wheat (11 x 9 mm), oat (6 x 5 mm), and rye (10 x 6 mm), with a histamine-positive control (5 x 5 mm). An open application test of wheat flour on intact forearm skin reproduced the eczematous lesions 30 minutes later, as confirmed by biopsy. Total IgE was 570 kU/L. Specific serum IgE by the ImmunoCAP system (Thermo Fisher Scientific) was positive for wheat (40 kU/L, class 5), barley (43 kU/L, class 5), and oat (16.8 kU/L, class 3) and negative (class 0) to α-amylase. Specific IgE by the ISAC system (Thermo Fisher Scientific) was negative for n-Tri a 18, gliadin, and rTri a 19 (ω-5 gliadin). In addition, specific IgE to rTri a 14 (wheat lipid transfer protein) and CM3+CM16 (wheat tetrameric α-amylase inhibitor), determined using the ADVIA-Centaur platform, was also negative. Immunoblotting with wheat flour extract revealed mainly IgE-binding bands at 11, 16, 42 and 60 kDa. No IgE-binding was detected against purified gliadin (Figure). Anti-IgE monoclonal antibodies (omalizumab) at 225 mg every 2 weeks were tested [6]. The patient experienced progressive improvement of his lesions, without additional treatment, from the first month of administration. Mild eczematous lesions reappeared a few days before his next fortnightly omalizumab doses.

However, 4 months later he was completely free of skin lesions and the Skin Quality of Life Questionnaire (Skindex-29) [7,8] showed an improvement compared with...
baseline (score of 47/145 vs 118/145). After 9 months, the omalizumab treatment intervals were extended to every 3 weeks and, currently (3 months later), the patients’ condition remains under control.

Wheat contact dermatitis should be considered in cases of chronic eczema in bakers, especially if they are atopic. Wheat proteins can be classified into salt-soluble fractions (albumins and globulins, accounting for 15%-20% of total proteins) and salt-insoluble proteins or prolamins (gliadins and glutenins). Various water-salt–insoluble wheat flour proteins appear to be involved in baker’s asthma [3]. However, IgE against these kind of proteins cannot be detected in our patient because of successful asthma treatment with specific wheat immunotherapy.

The immunoblotting study suggests that progressive and severe wheat contact dermatitis could be related to other proteins present in the salt-soluble fraction (eg, wheat 27-kDa allergen, peroxidase, and purple acid phosphatase), studied by Matsuo et al [4]. The pathogenesis of these IgE-binding proteins should be treated with a different drug, capable of inhibiting mediator release from T cells, mast cells, and basophils as well as antigen presentation by dendritic cells. It should prevent early- and late-phase allergic reactions of the skin and lungs.

We chose omalizumab, which has been used in severe asthma and urticaria [5], based on its mechanism of action: binding to the Fc region of all forms of circulating IgE, thereby preventing IgE-mediated reactions, and downregulation of high-affinity IgE receptor by binding to and inactivating IgE. To our knowledge, omalizumab has not been previously tested in protein contact dermatitis. The satisfactory cutaneous results and the improvement in the quality of life of our patient suggest its participation in these complementary immunomodulator effects.

Of note in our case was the coexistence of 2 forms of occupational baker’s entities: asthma and protein contact dermatitis. The pathogenesis of baker’s asthma is an IgE-mediated type I hypersensitivity with a clear response to specific wheat immunotherapy. Protein contact dermatitis is considered a combination of type I and delayed type IV allergic reactions with the involvement of other wheat allergens. In our patient, the wheat contact dermatitis skin lesions were resistant to specific immunotherapy and the standard symptomatic treatments were not useful.

The successful results reported in this article provide new insights into the therapeutic options for severe uncontrolled occupational protein contact dermatitis when allergen avoidance is not possible and other treatments are ineffective or unsuitable due to side effects.

Acknowledgments

We are grateful to Dr Lys Herraez Herrera, Medical Advisor from Novartis Pharmaceutical (Spain), for her valuable advice and critical reading of the manuscript.

Previous presentation

This work was presented as a poster at the International Symposium of Food Allergy, Barcelona 2011.

References


Manuscript received October 17, 2012; accepted for publication, December 7, 2012.

Pilar Mur Gimeno
Unidad de Alergia
C/ Malagón s/n
13500 Puertollano, Spain
E-mail: murgimenopilar@gmail.com

© 2013 Esmon Publicidad