

Novel causes of drug-induced occupational asthma



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Clinical Implications

- Occupational asthma is a common form of occupational lung disease in industrialized countries. We report 4 cases of occupational asthma demonstrated by specific inhalation challenge to sensitizing pharmaceutical agents not previously described in the literature: minoxidil, ferrimanitol ovalbumin, clarithromycin, and glucosamine-hydrochloride.

TO THE EDITOR:

Work-related asthma comprises occupational asthma (OA), which is caused by work, and work-exacerbated asthma, in which existing asthma is worsened by conditions in the workplace.¹ OA is currently one of the most common types of occupational lung disease in industrialized countries.²

Investigation of work-related asthma first aims to demonstrate the presence of asthma and then objectively confirm its relationship to work.¹ Diagnosing OA involves combining functional and inflammatory markers alongside environmental and immunological methods in a stepwise fashion.^{1,2} Briefly, diagnostic workup includes taking a detailed clinical and environmental history,

demonstrating bronchial hyperresponsiveness, and performing skin testing or serologic measurement of specific IgE antibodies. Bronchial inflammatory markers (ie, exhaled nitric oxide [FENO], analysis of induced sputum [IS]) may also be useful.³ Specific inhalation challenge (SIC) is the criterion standard technique for OA diagnosis.⁴ These tests are indicated for the study of new causes of OA and in determining the precise etiologic agent.

OA has been reported in pharmaceutical manufacturing workers exposed to different drugs, and as of 2016, 37 different drugs have been implicated.⁵ A systematic review of OA in antibiotic manufacturing workers by Díaz-Angulo et al⁶ found 36 cases reported in relation to different antibiotics.

In this article, we report 4 cases of SIC-demonstrated OA to 4 different pharmaceutical-sensitizing agents not previously described in the literature: minoxidil, ferrimanitol ovalbumin (FMOA), clarithromycin, and glucosamine-hydrochloride.

All patients were evaluated at our outpatient clinic following the same respiratory workup described in Figure 1. This protocol has been used in previous studies by our group.⁷ The results for each patient are presented in Table I.

The first patient is a 49-year-old atopic female beautician with allergic rhinoconjunctivitis due to grass and tree pollen as well as dog dander. Her regular duties consisted of spraying a 5% minoxidil solution to the scalp of alopecic clients. After 1 year and 4 months of employment, she developed itchy eyes, rhinitis, and persistent dry cough, which worsened to include dyspnea and eczema on her hands during the month preceding consultation. The complete study (performed while on leave from work), represented in Table I, led to a diagnosis of OA triggered by minoxidil. Measurement of eosinophils in IS was performed as previously described.⁷

Minoxidil causes hypertrichosis as a side effect after 3 to 6 weeks of use. This application led to its topical use to treat androgenic alopecia. As an occupational allergic disease, there is 1 existing case report of a hairdresser with eczema on the hands.⁸

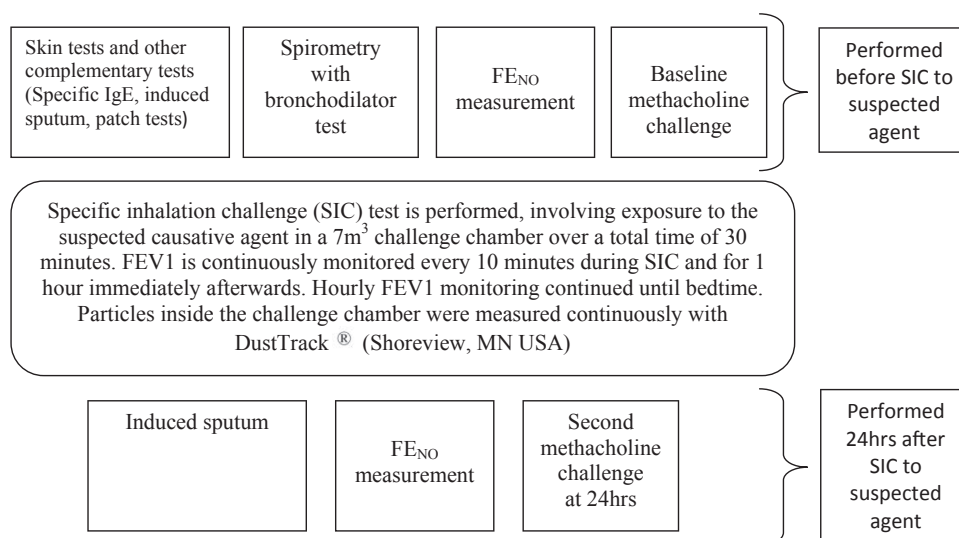


FIGURE 1. Workup performed in patients.

TABLE I. Test results for patients studied

Agent	Pre-SIC			SIC	24-h post-SIC		
	Complementary studies	Methacholine	FENO		Complementary studies	Methacholine	FENO
Minoxidil	1. Negative prick by prick (PP) testing with 5% minoxidil 2. Negative patch testing with minoxidil powder on petrolatum (5%), 5% minoxidil foam, and other components included in topical minoxidil 3. Normal spirometry 4. Baseline IS eosinophils 5%	Positive; PC ₂₀ : 0.8 mg/mL	Normal; 20.5 ppb	Negative	1. IS eosinophils 15%	Positive; PC ₂₀ 0.18 mg/mL	No changes
FMOA	1. Negative prick test result with egg and egg components 2. Normal spirometry with positive bronchodilator (BD) response (15% and 700 mL)	Positive; PC ₂₀ 0.31 mg/mL	High; 105 ppb	Positive: Immediate asthmatic response (30% fall in FEV ₁) after an accumulated time of 3 min at a concentration of 0.123 mg/m ³	1. SDS-PAGE was performed with FMOA, showing a protein band with an approximate molecular weight of 200 kDa. Subsequently, an IgE Western blot analysis with the patient's serum was conducted, showing a single IgE-binding band of 200 kDa	Positive; PC ₂₀ 0.125 mg/mL	High; 145 ppb
Clarithromycin	1. Negative PP with azithromycin, clarithromycin, and erythromycin 2. Normal spirometry with negative BD test result	Negative; PC ₂₀ > 16 mg/mL	Normal; 19 ppb	A positive late fall in FEV ₁ of 20% at 4 h after SIC was recorded and with improvement after the use of a short-acting beta-agonist	None	Negative; PC ₂₀ > 16 mg/mL	No changes
Glucosamine-hydrochloride	1. Negative PP with glucosamine-hydrochloride 2. Normal spirometry with negative BD test result	Positive; PC ₂₀ 1.25 mg/mL	High; 45 ppb	A positive late fall in FEV ₁ of 20% at 6 h after SIC was recorded and with improvement after the use of a short-acting beta-agonist	None	Positive; PC ₂₀ 1.25 mg/mL	High; 65 ppb

The second patient is a 34-year-old man with allergic rhinitis to grass pollen who worked for a pharmaceutical company. As part of his responsibilities over 6 years of employment, he provided technical support for several departments in the company. Over the previous 5 years, he noticed symptoms of rhinitis and dyspnea immediately after being exposed to FMOA. Exposure to FMOA in powder form in the workplace elicited an immediate asthmatic reaction (Table I).

Based on the positive prick-prick result with FMOA, an IgE Western blot analysis with the patient's serum was conducted, showing a single IgE-binding band of 200 kD (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). FMOA (molecular weight 200 kDa) is an oral iron supplement used for the treatment of iron-deficiency anemia. Therefore, to our knowledge, this is the first reported case of a patient with IgE-mediated occupational allergic asthma due to FMOA demonstrated by SIC.

Our third patient is a 35-year-old man referred to our department because of symptoms of dyspnea, dry cough, and itchy throat immediately after exposure to clarithromycin over the previous 4 months. As one of his assigned duties over the previous 4 years at his place of work, a pharmaceutical company, he weighed raw materials for pharmaceutical products to be packaged or pressed. While on leave from work, SIC with clarithromycin elicited a late reaction (Table I).

Clarithromycin is a macrolide antibiotic that acts on the inhibition of intracellular protein synthesis, halting bacterial growth. Several macrolides have been described as causing OA,⁶ but no case due to clarithromycin has been reported to date.

The fourth patient is a 42-year old woman who complained of dyspnea and cough of 1 year's duration, appearing in the late afternoon hours on days in which she cleaned a machine used for packaging glucosamine-hydrochloride. At the time of consultation, she had worked as a janitor for the company for 4 years. The SIC performed while she was on sick leave from work elicited a late reaction. In Europe, glucosamine is a drug approved for the treatment of osteoarthritis. No occupational disease has been reported because of exposure to glucosamine-hydrochloride.

Four new pharmaceutical agents—minoxidil, FMOA, clarithromycin, and glucosamine-hydrochloride—are described as causes of OA. All patients reported here were diagnosed using SIC, the criterion standard for agents causing OA.⁴ In 3 cases, the agents induced a significant early or late fall in FEV₁. In patient 1, diagnosis of OA was suggested because of a significant decrease in methacholine PC₂₀⁴ and an increase in eosinophils in IS after challenge.⁹ Significant variations in methacholine PC₂₀ were also observed in patient 2 after an early reaction. In patient 3, baseline methacholine was negative, likely because the patient had been on sick leave for several months. The patient then remained negative after a bronchial late reaction; though rare, this response has been described previously.¹⁰ A significant increase in FENO (>20% from baseline) after positive SIC was observed only in patients 2 and 4. This is in agreement with a previous study⁴ in which the increase in FENO was not observed in all cases after positive SIC. FENO may aid in the interpretation

of SIC in some cases, though it cannot be used generally as a surrogate marker to predict or assess SICs with occupational agents.

Since diagnosis, all patients were relocated to avoid exposure to the offending agent, as recommended by current guidelines. In accordance with published evidence, ingestion or use of these therapeutic agents was contraindicated.¹ This report of 4 cases expands the list of agents that can induce sensitization in exposed workers and underscores the importance of SIC as a diagnostic tool.

Acknowledgments

We thank Oliver Shaw, PhD, for editorial assistance.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 20, 2018; revised July 10, 2018; accepted for publication July 12, 2018.

Available online August 1, 2018.

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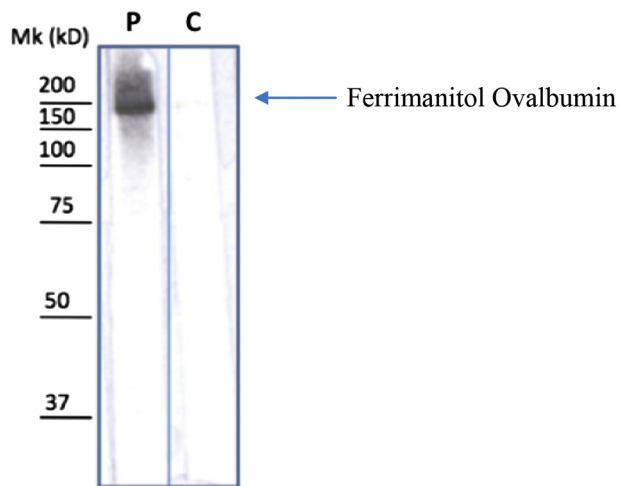
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<https://doi.org/10.1016/j.jaip.2018.07.026>

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ONLINE REPOSITORY



P: Patient's serum

C: Control serum

Mk: Molecular markers

FIGURE E1. IgE Western blot analysis of FMOA with the patient's serum, showing a single IgE-binding band of 200 kD. A control serum gave no binding bands.