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Occupational asthma from sensitisation to 4,4-methylene-bismorpholine in clean metalworking fluid

To the Editor:

European Respiratory Society guidelines on the management of work-related asthma recommend that occupational asthma with an allergic mechanism should be diagnosed by both identifying the workplace as the cause, and confirming sensitisation to the asthmagen by specific inhalational challenge (SIC), in the absence of any available specific IgE tests [1, 2]. Used (contaminated) metalworking fluid is the usual cause of occupational asthma in exposed workers. We present the first case of occupational asthma due to the biocide additive 4,4-methylene-bismorpholine present in clean metalworking fluid.

A 54-year-old Kenyan male presented with a 2-year history of rhinitis, wheeze, dry cough and chest tightness, which were worse at night and while at work, and improved away from work on holiday. He had had rhinitis from grass pollen, perfumes and cleaning agents intermittently for 15 years, and acne due to metalworking fluid 5 years previously. There was no childhood or family history of asthma and he had never smoked cigarettes. He had been employed as a machine tool setter operator for 22 years manufacturing car axles. For the past 6 years he had worked on an enclosed computer numerical controlled milling, drilling and boring machine, with its own oil sump, using carbide-tipped tools. It was loaded by a robot but there was no delay between the end of machining and door opening, which produced a visible mist about 3 m from his work station. The machines used Fuchs Ecocool Ultralife A, a semi-synthetic metalworking fluid for aluminium alloys. Clinical examination and chest radiograph were unremarkable. Skin-prick allergy testing (SPT) revealed a 0 mm reaction to 0.9% saline and a 7 mm reaction to histamine hydrochloride 10 mg·mL^{-1}. There were positive reactions to grass pollen (8 mm), dog dander (5 mm), cladosporium (4 mm) and 4,4-methylene-bis-morpholine (3 mm), with borderline reactions to 5 mg·mL^{-1} cobalt chloride (2.5 mm) and clean metalworking fluid (2.5 mm). Total IgE was 2048 kU·L^{-1}, white blood cell count 7.81×10^9 L^{-1} and eosinophil count was raised at 0.75×10^9 L^{-1}. Two-hourly peak flow measurements made at home and work over 4 weeks were analysed using OASYS [3, 4]. The OASYS score was 3.4 and the area between the curves score was 23.4 L·min^{-1}·h^{-1} confirming a significant work effect (fig. 1a). Spirometry revealed a borderline obstructive ventilatory defect (forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio 70%) with normal indices (FEV_1 2.75 L, 86% predicted; FVC 3.95 L, 100% predicted). While work-exposed, his fractional exhaled nitric oxide (F_{ENO}) was raised at 71 ppb [5, 6] and nonspecific bronchial responsiveness (NSBR) to methacholine was normal (>4800 µg by the Yan method [7]).

He underwent SIC after 3 weeks away from work. He was challenged with 7% clean Ecocool Ultralife A metalworking fluid in water for a total of 50 min *via* a Turboneb II (Clement Clarke International Ltd, Harlow, UK) and Maxineb (Flexicare Medical Ltd, Mountain Ash, UK) nebuliser. Initial FEV_1 was 2.63 L, which fell immediately by 20%, recovering after 15 min, and fell again at 3–11 h by 29.7%, accompanied by asthmatic symptoms. Subsequent SIC to 0.7% 4,4-methylene-bismorpholine in water (Chemical Abstract Service (CAS) registry number 5625-90-1; occupational asthma hazard index 0.98) for a total of 50 min resulted in immediate sustained rhinitis symptoms, then a late fall in FEV_1 of 16.5% from 2.36 L, at 9–11 h after challenge (fig. 1b). He had a more than four-fold increase in NSBR to methacholine (pre-SIC cumulative dose that caused a 20% fall in FEV_1 (PD_{20}) >4800 µg; 24-h post-SIC PD_{20} 587 µg), but no clinically significant change in F_{ENO} (F_{ENO} pre-SIC 77 ppb; post-SIC 70 ppb). He had negative SICs to the solvent 2,2-aminoethoxyethanol (CAS registry number 929-06-6; occupational asthma hazard index 0.41), pH stabiliser 2-di-butylaminoethanol (CAS registry number 102-81-8; occupational asthma hazard index 0.95)

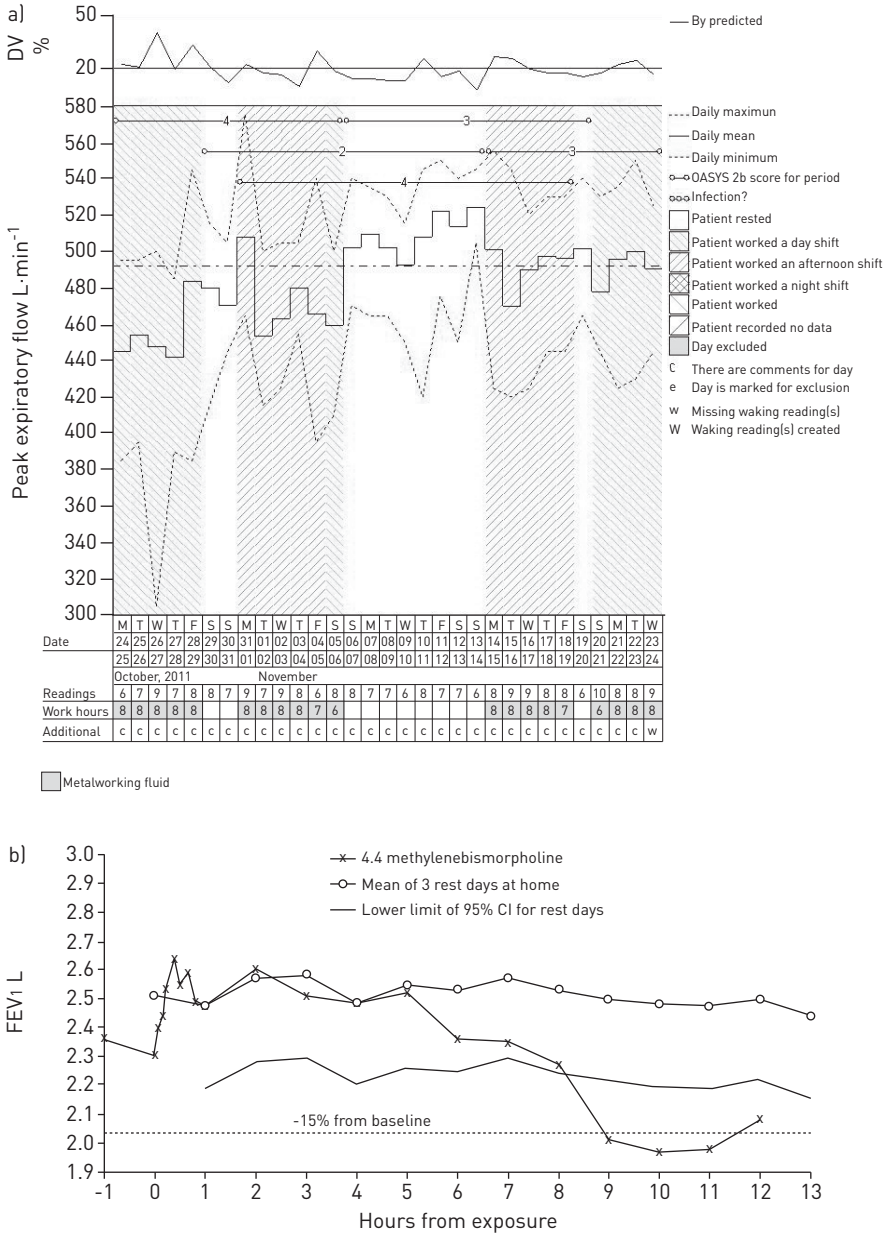

FIGURE 1 a) OASYS analysis of serial peak flow measurements made using a Mini-Wright digital peak flow meter, and showing definite occupational asthma. The top part of the chart shows the diurnal variation (DV) for each day, the middle of the chart shows the maximum, mean and minimum peak flow. The bottom of the record shows the days, dates and number of readings per day for the record. b) Specific inhalational challenge showing a late asthmatic reaction to 0.7% 4,4-methylene-bismorpholine, with a sustained late fall in forced expiratory volume in 1 s (FEV_1) of 16.5% at 9 h post-challenge.

and cobalt chloride 5 mg·mL^{-1}. A suitable unexposed workplace could not be found and 9 months later he remained unemployed with ongoing asthma symptoms. He required treatment with 200 µg inhaled beclometasone *b.d.* with an FEV_1 of 2.59 L (82% predicted), FVC of 4.45 L (113% predicted) and F_{ENO} 56 ppb.

The positive SIC and greater than four-fold increase in NSBR to methacholine supports the diagnosis of occupational asthma from sensitisation due to 4,4-methylene-bismorpholine. GEIER *et al.* [8] have previously demonstrated dermatological sensitisation to a number of structurally related biocide additives, including 1% 4,4-methylene-bismorpholine by skin patch testing. However, a number of features need to be accounted for. The baseline F_{ENO} was measured during work exposure and was high, as was the pre-SIC F_{ENO} after 3 weeks away from work, but was lower after 9 months without exposure. These values may have been confounded by atopy and rhinitis [5, 9]. Some have found a significant increase in F_{ENO} following a late asthmatic reaction;

however, a significant proportion of low molecular weight occupational asthmagens produce a non-eosinophilic asthma variant [10] and, although we did not obtain sputum cell counts, this may explain the lack of $F_{E}NO$ change. All measurements were carried out according to European Respiratory Society/American Thoracic Society guidelines [11] using the NioxMino handheld machine (Aerocrine AB, Solna, Sweden). A 3 mm SPT to 4,4-methylene-bismorpholine does not provide conclusive evidence of an IgE-mediated mechanism; indeed, the absence of demonstrable specific IgE antibodies in subjects with occupational asthma caused by low molecular weight agents has made many suspect non-IgE mediated mechanisms [12].

Metalworking fluids are used to reduce heat and friction in industrial metalworking operations, and are complex mixtures of oils, emulsifiers, alkaline pH buffers, biocides and other additives. Once used, metalworking fluids may be contaminated with bacterial and fungal microbes, hydraulic fluid, added biocides, dissolved metals and other manufacturing by-products, all of which are potential sensitisers for occupational asthma, as well as causes of extrinsic allergic alveolitis, humidifier fever and occupational bronchitis [13, 14]. SIC testing to metalworking fluids has been undertaken safely, though positive tests are much more common to used metalworking fluids than to clean metalworking fluids [15, 16]. 4,4-methylene-bismorpholine has a high asthma hazard index (maximum 1.0) using the Manchester Occupational Asthma Hazard Programme, which has a high sensitivity in identifying novel asthmagens [17].

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Occupational asthma is caused by 4,4-methylene-bismorpholine, a novel asthmagen present in clean metalworking fluid http://ow.ly/nuttg

Gareth I. Walters, Vicky C. Moore, Alastair S. Robertson, Emmet E. McGrath, Edward Parkes and P. Sherwood Burge
Occupational Lung Disease Unit, Birmingham Chest Clinic, Birmingham, UK.

Correspondence: G.I. Walters, Occupational Lung Disease Unit, Birmingham Chest Clinic, Great Charles Street, Birmingham, B3 3HX, UK. E-mail: gaxwalters@hotmail.com

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