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Letter to the Editor

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

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Short title

Occupational asthma from clean metalworking fluid

Keywords

Biocides, metalworking fluid, oils, asthma, occupational asthma, bronchial challenge, bismorpholine

Capsule summary

This is the first case of occupational asthma due to a biocide 4, 4-methylene-bismorpholine used in clean metalworking fluid, confirmed by a positive specific inhalational challenge.

Competing Interests

None of the authors have any competing interests

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To the Editor,

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

A 54-year old Kenyan man presented with a 2-year history of rhinitis, wheeze, dry cough and chest tightness, which were worse at night and whilst 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 MWF 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 last 6 years he had worked on an enclosed computer numerical controlled (CNC) 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 metres from his work station. The machines used Fuchs Ecocool Ultralife A, a semi-synthetic MWF for aluminium alloys. Clinical examination and chest radiograph were unremarkable. Skin-prick allergy testing (SPT) revealed a 0mm reaction to 0.9% saline and a 7mm reaction to histamine hydrochloride 10mg/ml. There were positive reactions to grass pollen (8mm), dog dander (5mm), cladosporium (4mm) and 4, 4-methylene-bis-morpholine (3mm), with borderline reactions to 5mg/ml cobalt chloride (2.5mm) and clean MWF (2.5mm). Total IgE was 2048kU/L, white blood cell count 7.81×10^9/L and eosinophil count was raised at 0.75×10^9/L. 2-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 ABC score 23.4 litres/min/hour confirming a significant work effect (Figure 1). Spirometry revealed a borderline obstructive ventilatory defect (FEV_1/FVC=70%) with normal indices (FEV_1=2.75L (86% predicted); FVC=3.95L (100% predicted). While work-exposed, his fractional exhaled nitric oxide (FE_{NO}) was raised at 71ppb [5, 6] and non-specific bronchial responsiveness (NSBR) to methacholine was normal (>4800mcg by the Yan method [7]).

He underwent specific inhalational challenge (SIC) after 3 weeks away from work. He was challenged with 7% clean Ecocool Ultralife A MWF in water for a total of 50 minutes via a Turboneb II and Maxineb 90 nebulizer. Initial FEV_1 was 2.63L, which fell immediately by 20%, recovering after 15 minutes, and fell again at 3-11 hours 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; OA Hazard Index=0.98) for a total of 50 minutes resulted in immediate sustained rhinitis symptoms, then a late fall in FEV_1 of 16.5% from 2.36L, at 9-11 hours after challenge (Figure 2). He had a >4-fold increase in NSBR to methacholine (pre-SIC PD_{20}>4800mcg; 24-hour post-SIC PD_{20}=587mcg), but no clinically significant change in FE_{NO} (FE_{NO} pre-SIC=77ppb; post-SIC=70ppb). He had negative SICs to the solvent 2, 2-aminoethoxyethanol (CAS registry number 929-06-6; OA Hazard Index=0.41), pH stabilizer 2-di-butylaminoethanol (CAS registry number 102-81-8; OA Hazard Index=0.95) and cobalt chloride 5mg/ml. A suitable unexposed workplace could not be found and nine months later he remained unemployed with ongoing asthma symptoms. He required treatment with 200 micrograms of inhaled beclometasone b.d. with an FEV_1 of 2.59L (82% predicted), FVC of 4.45L (113% predicted) and FE_{NO} 56ppb.

The positive SIC and greater than 4-fold increase in NSBR to methacholine supports the diagnosis of OA from sensitization due to 4, 4-methylene-bismorpholine. Geier et al. have previously demonstrated dermatological sensitization to a number of structurally related biocide additives, including 1% 4, 4-methylene-bismorpholine by skin patch testing [8]. However, a number of features need to be accounted for. The baseline FE_{NO} was measured during work-exposure and was high, as was the pre-SIC FE_{NO} 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 FE_{NO} following a late asthmatic reaction; however a significant proportion of low molecular weight (LMW) occupational asthmagens produce a non-eosinophilic asthma variant [10] and although we did not obtain sputum cell counts, this may explain the lack of FE_{NO} change. All measurements were carried out according to ERS/ATS guidelines [11] using the NioxMino handheld machine (Aerocrine AB, Solna, Sweden). A 3mm 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 OA caused by LMW agents has made many suspect non-IgE mediated mechanisms [12].

MWFs 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, MWFs may be contaminated with bacterial and fungal microbes, hydraulic fluid, added biocides, dissolved metals and other manufacturing by-products, all of which are potential sensitizers for OA, as well as causing extrinsic allergic alveolitis, humidifier fever and occupational bronchitis [13, 14]. SIC testing to MWF has been undertaken safely, though positive tests are much more common to used- than clean MWF [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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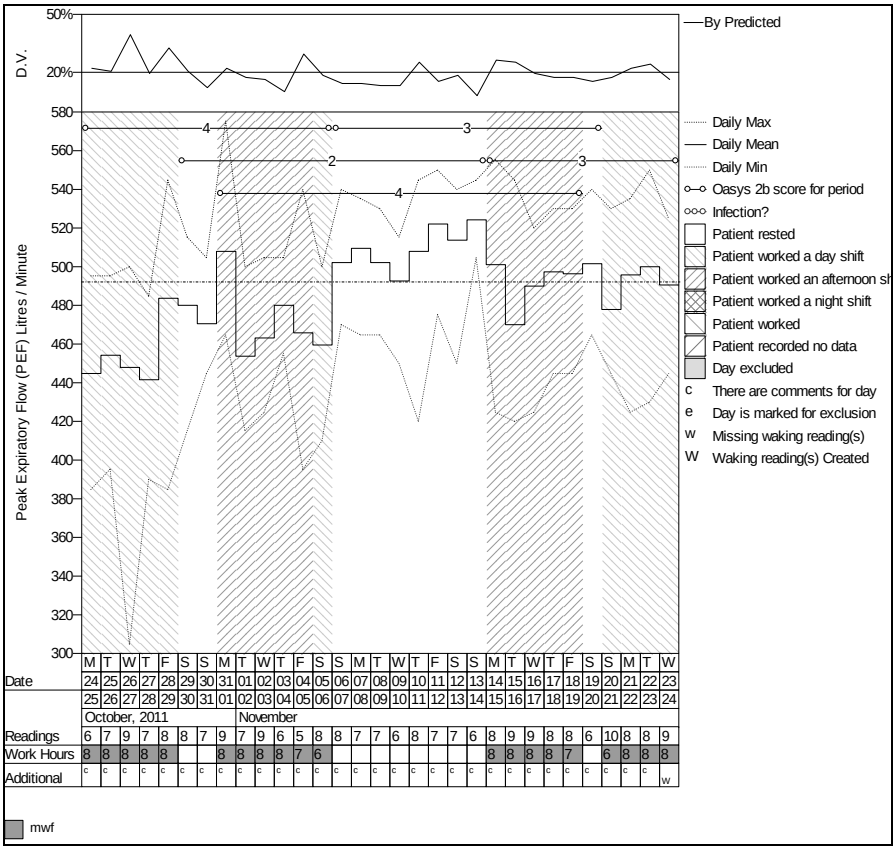

Figure 1. OASYS analysis of serial peak flow measurements made using a Mini-Wright digital peak flow meter, andshowing definite occupational asthma. The top part of the chart shows the diurnal variation for each day, the middle of the chart shows the maximum-, mean- and minimum peak flow. The bottom of the record shows the days, dates and number of readings per day for the record.

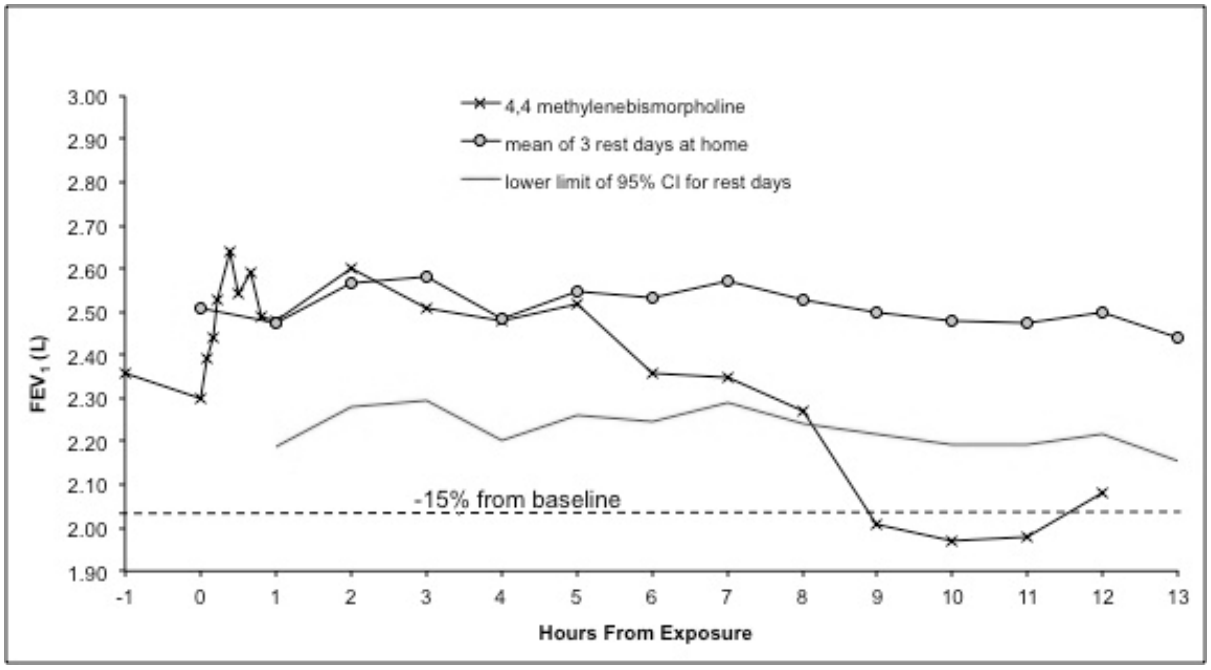

Figure 2. Specific inhalational challenge showing a late asthmatic reaction to 0.7% 4, 4-methylene-bismorpholine, with a sustained late fall in FEV_1 of 16.5% at 9 hours post-challenge.

Twitter feed summary

We report occupational asthma caused by 4, 4-methylene-bismorpholine, a novel asthmagen present in clean metalworking fluid.