

Case Report

Occupational Asthma Related to Low Levels of Airborne Methylene Diphenyl Diisocyanate (MDI) in Orthopedic Casting Work

Hille Suojalehto, MD,^{1*} Irmeli Linström, MD,¹ Maj-Len Henriks-Eckerman, Lic Tech,²
Soile Jungewelter, MD,³ and Katri Suuronen, PhD³

Orthopedic plaster casts contain methylene diphenyl diisocyanate (MDI). A few case reports have suggested occupational asthma to MDI in casting work. However, the knowledge of the exposure levels related to the occupational asthma cases is lacking.

We report on two occupational asthma cases due to MDI in nurses irregularly applying orthopedic plaster casts, verified with placebo controlled specific inhalation challenge. The levels of MDI in the air were measured in the exposure chamber during the specific inhalation challenges with a quantitative method including filter collection and subsequent liquid chromatography-mass spectrometry (LC-MS) analysis of the isocyanate groups. In order to estimate the level of airborne MDI in casting work, measurements were conducted also in two hospitals during the application and removal of synthetic plaster casts using the same method. The concentrations were well below the occupational exposure limit in both specific inhalation challenge and hospital measurements.

Based on our findings, even minor exposure to airborne MDI in casting work can cause an asthmatic reaction in some patients. Am. J. Ind. Med. © 2011 Wiley Periodicals, Inc.

KEY WORDS: occupational asthma; isocyanates; methylene diphenyl diisocyanate; MDI; plaster casts; specific inhalation challenge test; specific bronchial provocation test

INTRODUCTION

Modern orthopedic plaster casts are commonly based on synthetic plastic that contains up to 25% methylene diphenyl diisocyanate (MDI). Therefore, health care workers in casting operations may be exposed to MDI, which, like other diisocyanates, is a well-known asthma causing agent [Vandenplas et al., 1993; Bello et al., 2004]. The use of plaster casts has grown in recent years, and nowadays they are the most commonly used casting materials in Finland. Some case studies have reported isocyanate asthma in workers handling plaster casts [Tanaka et al., 1994; Sommer et al., 2000; Donnelly et al., 2004]. We report on two cases of occupational asthma due to MDI, confirmed by specific inhalation challenge, in nurses applying orthopedic plaster casts to patients. In addition, we report measurement results of airborne MDI during specific

Abbreviations: 2-MP, 2-methoxyphenylpiperazine; BD, bronchodilator medication; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid; ISO, International Organization for Standardization; LC-MS, liquid chromatography-mass spectrometry; MDI, methylene diphenyl diisocyanate; NCO, isocyanate group; OEL, occupational exposure limit; PD₁₅FEV₁, provocative dose causing a reduction of 15% in FEV₁; PEF, peak expiratory flow; PVC, polyvinyl chloride.

¹Control of Hypersensitivity Diseases Team, Finnish Institute of Occupational Health, Helsinki, Finland

²Chemical Agents Team, Finnish Institute of Occupational Health, Helsinki, Finland

³Occupational Medicine Team, Finnish Institute of Occupational Health, Helsinki, Finland

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Written and signed consent has been obtained from both patients.

*Correspondence to: Dr. Hille Suojalehto, MD, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A 00250 Helsinki, Finland. E-mail: hille.suojalehto@ttl.fi

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inhalation challenge in the exposure chamber as well as during normal casting work and casting simulation.

CASE REPORTS

Case 1

Patient 1 was a 44-year-old non-smoking female nurse who had worked in the first aid unit of the hospital since 1989. Since the beginning of 1990s she applied and removed up to three plaster casts per day, but also had days without casting. She used latex or polyvinyl chloride (PVC) gloves when applying and removing casts. She had earlier suffered from mild seasonal rhinitis symptoms. In 1994 she had her first severe dyspnoea attack that was treated with adrenaline and corticosteroid in the intensive care unit. A few hours before the attack, a plaster cast had been applied to her own leg as a part of her training. Asthma was diagnosed in 1999; in 1999–2005 she had three additional severe dyspnoea attacks during working days. She also had less severe symptoms regularly and therefore needed asthma medication when working. During her maternity leave in 2001 she had no asthma symptoms.

The patient was referred for further examinations in 2006. Sensitization to workplace agents, foodstuffs, and common environmental allergens were extensively tested using skin prick tests and allergen specific IgE; these were all negative. Specific IgE tests and skin prick tests to diisocyanates and latex were also negative. Tests of hereditary angioedema (C1 esterase inhibitor, C3, and C4) were normal. Lung function tests were performed when the patient was on sick leave, still using inhaled corticosteroid medication. Baseline spirometry was normal, forced expiratory volume in 1 s (FEV_1) was 2.74 l (84% predicted). Fractional exhaled nitric oxide (FENO) level was normal, 5.55 ppb (normal limit 30 ppb). A histamine challenge test showed moderate nonspecific bronchial hyperresponsiveness, the dose of histamine that caused a 15% decrease in FEV_1 ($PD_{15}FEV_1$) [Sovijarvi et al., 1993] being 0.32 mg (threshold for positive test 1.6 mg). Serial peak expiratory flow (PEF) monitoring while the patient was on inhaled corticosteroid medication showed suggestive worsening of peak flow during working days.

Inhaled corticosteroids were discontinued 2 days before the specific inhalation challenge. The patient was admitted to the specific inhalation challenge first with placebo and then MDI. The tests were carried out in a 6 m³ challenge chamber over two subsequent days, each with a 24-hour follow-up. In the placebo test, 2 ml of a control solution (containing 5 mg/ml sodium chloride, 4 mg/ml phenol, and 2.75 mg/ml sodium bicarbonate in sterile water) was sprayed into the chamber at the beginning of the test, after which the patient stayed in the chamber for 15 min. The MDI test was performed in a

similar way: 1.5 ml solution of 0.32 mg/ml MDI in toluene was sprayed into the challenge chamber and the patient stayed in the chamber for 15 min. The mean concentration during the specific inhalation challenge given as NCO (isocyanate groups) was low, 0.17 $\mu\text{g NCO}/\text{m}^3$, which corresponds to 0.51 $\mu\text{g}/\text{m}^3$ (0.00005 ppm) monomeric MDI. Figure 1 shows the results of the placebo and MDI challenge tests; the FEV_1 fell by a maximum of 25% from the base line after 1 hr. An early reaction was observed; because of the history of severe reactions, bronchodilator and an oral steroid were given immediately after the reaction occurred. Late reaction was not detected. Based on the result of specific inhalation challenge the occupational asthma diagnosis was made and the patient was removed from casting work.

Six months after removal from casting work, hyper-responsiveness was mild ($PD_{15}FEV_1$ 0.69 mg). Three years after removal from casting work Patient 1 still needed continuous asthma medication (budesonide 800 $\mu\text{g}/\text{day}$, formoterol and montelukast) and an oral corticosteroid during respiratory infections, but no further severe dyspnoea reactions had occurred.

Case 2

Patient 2 was a 35-year-old male nurse, who had a previous five pack-year smoking history. He had atopic eczema in childhood. He had worked in an orthopedic operating theatre since 1998. Since 2003 he applied and removed up to two orthopedic plaster casts per day, but

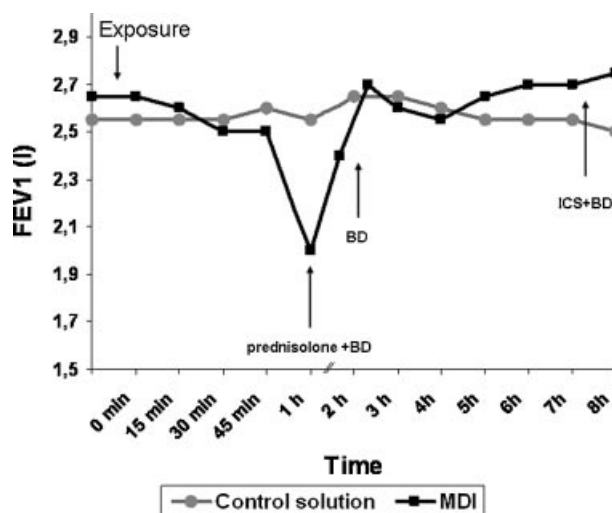


FIGURE 1. Results of the specific inhalation challenge for Patient 1 illustrating the changes in the FEV_1 after exposure to placebo (control solution) and methylene diphenyl diisocyanate (MDI). The mean MDI concentration during the specific inhalation challenge was 0.17 $\mu\text{g NCO}/\text{m}^3$, i.e. 0.51 $\mu\text{g}/\text{m}^3$ (0.00005 ppm) monomeric MDI. The patient was treated with bronchodilator medication (BD), prednisolone, and inhaled corticosteroid (ICS).

also had working days with no casting. He used disposable nitrile or latex gloves when applying casts, but no gloves when removing casts. Six years after starting his work he developed rhinitis and 2 years after this a work-related cough and dyspnoea. Asthma was diagnosed in 2007 and an inhaled steroid was introduced.

Serial PEF monitoring showed deterioration when working in the operating theatre; because of occupational asthma suspicion he was removed from casting work and referred for further examinations in 2008. Skin prick tests to grass pollen was positive, but all other common environmental and work-related allergens, including latex and diisocyanates, were negative. Specific IgE test to diisocyanates was also negative. The patient remained on inhaled corticosteroid medication during the lung function tests and the specific inhalation challenge. Spirometry showed mild obstruction in small airways (maximal expiratory flow at 50% of vital capacity 3.24 l, 54% predicted; FEV₁ 4.29 l, 88% predicted). Bronchial hyperresponsiveness was moderate (PD₁₅ FEV₁ 0.37 mg) and FENO was normal (10.7 ppb). The specific inhalation challenge was carried out in the same way as with Patient 1, except that a more concentrated solution of MDI was used, the mean MDI concentration being 8.6 µg NCO/m³, i.e., 26 µg/m³ (0.0026 ppm) monomeric MDI. Figure 2 shows the results of the specific inhalation challenge. The patient had an early prolonged reaction, FEV₁ fell by a maximum of 42%, and asthma symptoms persisted for several days. No rhinitis reaction was observed. The specific inhalation challenge to latex gloves was negative. Based on the results of specific inhalation challenge to MDI, the diagnosis of occupational asthma was made.

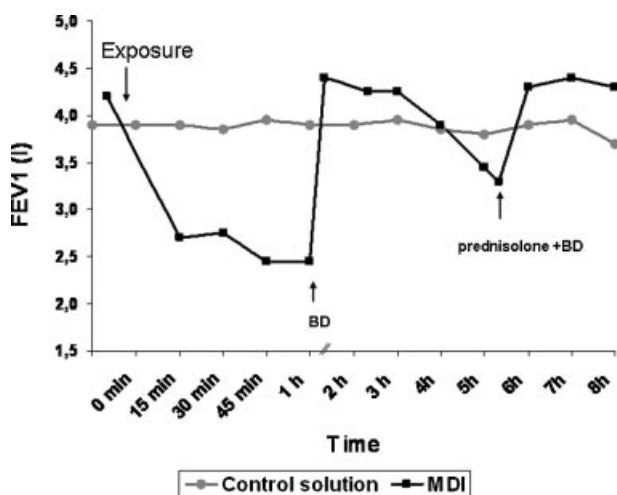


FIGURE 2. Results of the specific inhalation challenge for Patient 2 illustrating the changes in the FEV₁ after exposure to placebo (control solution) and methylene diphenyl diisocyanate (MDI). The mean MDI concentration during the specific inhalation challenge was 8.6 µg NCO/m³, i.e. 26 µg/m³ (0.0026 ppm) monomeric MDI. The patient was treated with bronchodilator medication (BD) and prednisolone.

Two years after he was removed from casting work, Patient 2's asthma symptoms had improved, but he was still on continuous asthma medication (Budesonide 400 µg/day).

Both of the patients gave written informed consent for the tests and publication of their case in the medical literature.

ASSESSMENT OF AIRBORNE MDI IN CASTING WORK

Methods

The same measurement method was used both in the specific inhalation challenge and in the hospital measurements and it consisted of the following: Airborne di- and triisocyanates were collected on a glass fiber filter impregnated with 2-methoxyphenylpiperazine (2-MP), at a sampling rate of 2 L/min. The 2-MP-derivatives of isocyanates were desorbed with acetonitrile and analyzed by liquid chromatography-mass spectrometry (LC-MS). The method is a modification of an International Organization for Standardization (ISO) standard [ISO 16702, 2001]. The concentration results include NCO groups from 4,4'-MDI, 2,4'-MDI and the main 3-ring prepolymer.

In order to estimate exposure levels in hospital work, we measured the diisocyanate concentration in the air during a casting simulation (the synthetic plaster cast was rolled over a piece of wood) and during normal casting work in two hospitals. The samples were taken from the breathing zone of the nurse and above the casting spot (distance about 15 cm) when applying and removing the cast. Sampling time in the breathing zone was 60 min (including phases with no casting) in the hospital measurements and 15 min in the simulation. The casting spot samples followed the normal casting cycles, and were thus collected from several 1–5 min phases, the total sampling time being 10–15 min.

ASSESSMENT OF AIRBORNE MDI IN CASTING WORK

Results

Table I shows the measured NCO concentrations in hospital casting work and a casting simulation. The concentrations were very low in both casting and removing cast, the results varying between 0.02 and 2.5 µg NCO/m³. The highest concentration was measured when simulating cast removing.

DISCUSSION

We have presented two cases of asthma due to MDI-containing orthopedic plaster casts in nurses, confirmed

TABLE I. Measured diisocyanate concentrations in the air during casting work with synthetic plaster casts given as the mass of functional isocyanate (NCO) groups

	Breathing zone ($\mu\text{g NCO}/\text{m}^3$)	Near casting spot ($\mu\text{g NCO}/\text{m}^3$)	Removing plaster cast, near sawing spot ($\mu\text{g NCO}/\text{m}^3$)
Casting simulation	0.11	0.52	2.5
Hospital 1—normal casting work	0.03*	0.77	0.02
Hospital 2—normal casting work	0.02*	0.25	Not measured

The Finnish occupational exposure limit (OEL) is $35 \mu\text{g}/\text{m}^3$ for NCO groups, which corresponds to about $100 \mu\text{g}/\text{m}^3$ (0.01 ppm) monomeric MDI.

*The sampling period includes phases with no casting work.

with placebo controlled specific inhalation challenge and workplace measurements of MDI. Occupational asthma caused by MDI in orthopedic plaster casts has also been reported by others [Tanaka et al., 1994; Sommer et al., 2000; Donnelly et al., 2004]. However, in the report of Donnelly et al., specific inhalation challenge was performed without placebo control, whereas the reports of Sommer and Tanaka could not be evaluated because they are not written in English.

Both of our patients had been applying plaster casts for several years before the first symptoms appeared. Casting was not their main job and they did it irregularly. Patient 1 had four severe dyspnoea attacks related to work. She had an early asthmatic reaction in the specific inhalation challenge with a very low concentration of MDI, while late reaction may have been inhibited by medication [Fabbri et al., 1985; Mapp et al., 1987]. After removal from casting work, no further severe reactions occurred. It is likely that the reactions at work were related to MDI exposure, possibly being late asthmatic reactions. Both of our patients needed regular asthma medication a few years after removal from MDI exposure. This is in line with previous findings of poor outcome of MDI-induced asthma [Piirila et al., 2000].

It has been suggested that respiratory sensitization could be accelerated by skin contact with diisocyanates [Bello et al., 2007]. Skin contact with unhardened plaster material was possible during casting and immediately after it, even though our patients regularly used disposable gloves. Based on the patients' own reports, skin contact seemed to be more frequent when removing the hardened cast. In the presented patient cases and the casting work measurements, it was impossible to estimate the amount of unhardened MDI that may pass through the protective gloves. Preliminary results from other groups indicate that even disposable gloves may protect workers from diisocyanates [Liu et al., 2007]. While MDI and other diisocyanates are known to cause allergic contact dermatitis [Liippo and Lammintausta 2008], the role of skin exposure in the development of diisocyanate asthma needs to be investigated in more detail.

In our study, the concentrations measured during both the hospital measurements and the specific inhalation challenge using a well-validated method, were well below the Finnish occupational exposure limit (OEL) of $35 \mu\text{g}/\text{m}^3$ for functional isocyanate (NCO) groups, which is in line with the respective European OELs.

The concentration of $35 \mu\text{g}/\text{m}^3$ NCO groups corresponds to about $100 \mu\text{g}/\text{m}^3$ (0.01 ppm) MDI molecules, assuming that all of the NCO groups originate from monomeric MDI. The isocyanate OELs and problems in their measurement metrics and unit conversion have been discussed elsewhere [Bello et al., 2004]. The cast removal produced a much higher MDI concentration in the simulation than did the hospital work probably because the casts were relatively newly made (a couple of days earlier), and therefore contained more functional isocyanate groups. Other possible reasons for the discrepancy in the results include variation in sawing manner and equipment, air turbulence within the measuring zone, and measuring distance from the sawing spot.

In the case of Patient 1, the target concentration in the specific inhalation challenge was set lower than usually because of her clinical history of severe reactions. In the case of Patient 2, the target concentration of MDI was set to the average level used in specific inhalation challenges at Finnish Institute of Occupational Health, this level being at about one third the OEL. Nevertheless, the commonly used target concentration in the specific inhalation challenge was found to be too high for this specific patient, resulting in a relatively strong reaction. Based on the present case 1 and our other experience of patients with diisocyanate asthma, it seems that even extremely low levels of MDI are enough to elicit asthmatic reactions in some patients. This inference is supported by other reports [Redlich, 2010]. However, the level of exposure inducing asthma in our patients remains unknown.

The fact that the specific inhalation challenge reactions were strong and took place at even very small concentrations compared with the OEL, suggests that the OEL for isocyanates is too high for MDI. In order to improve workers' safety, it is advisable to use plaster materials with low MDI content and to apply effective

ventilation measures and skin protection in all plaster casting work.

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