CASE STUDY

Sub-acute occupational hypersensitivity pneumonitis due to low-level exposure to diisocyanates in a secretary

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ABSTRACT: There is virtually no information in the literature about the exposure levels needed to induce hypersensitivity pneumonitis (HP) by diisocyanates. The present study reports a case of occupational HP due to diisocyanates after low-level exposure.

A 53-yr-old female never-smoker developed progressive shortness of breath on exertion, cough, fatigue and flu-like symptoms shortly after she began work as a secretary of a car body repair shop. A diagnosis of HP was made 2 yrs later, based on a restrictive ventilatory defect, a reticulo nodular and discrete ground-glass pattern on high-resolution computed tomography, lymphocytosis in bronchoalveolar lavage and specific immunoglobulin G antibodies to diisocyanate human serum albumin conjugates in the patient’s serum.

The diagnosis was confirmed by recovery after exposure cessation and deterioration after re-exposure. Ambient monitoring revealed air concentrations of different diisocyanate monomers below the detection limit in both the patient’s work station and in front of the paint spray booths, with the exception of one measurement that showed 4,4-methylene diphenyl diisocyanate concentrations of 3 μg·m⁻³ in front of one booth (corresponding to a total reactive isocyanate group concentration of 1 μg·m⁻³).

The present authors conclude that concentrations of diisocyanates far below current exposure limits may induce hypersensitivity pneumonitis in susceptible subjects.

KEYWORDS: Diisocyanates, hypersensitivity pneumonitis, occupational exposure

Diisocyanates are the most important single cause of occupational asthma in many countries [1]. While asthma is the most prominent disease, hypersensitivity pneumonitis (HP) induced by diisocyanates has been reported casually [2], but recent information suggests that in some workplaces, HP may be a more frequent consequence of diisocyanate exposure than originally thought [3]. Little is known about the exposure levels needed for the induction of HP by diisocyanates; one epidemiological study in a plant engineered for minimal exposure to diisocyanates did not report cases suggestive of HP [4].

A recent expert workshop concluded that data regarding dose–response relationships of diisocyanates on primary sensitisation are few and insufficient [1], this is particularly the case for HP.

CASE REPORT

A 53-yr-old female, nonatopic never-smoker had worked intermittently as a secretary of a car body repair shop since March 1999 and had been in regular employment until April 2000. The patient was otherwise healthy and was not taking any medication. She developed shortness of breath on exertion, cough, phlegm production, fatigue and nightly fever shortly after starting the job. In 2000, the symptoms progressed rapidly. These symptoms had a slowly progressive course, with no direct relationship to work, but did improve when the patient was on holiday. She had no prior or concomitant nonoccupational contact to diisocyanates or other known inducers of HP. In January 2002, the symptoms worsened and she quit work in May 2002 (fig. 1). A diagnosis of HP was made shortly afterwards in April/May 2002, ~3 yrs after the start of exposure. Auscultation yielded high-frequency end-inspiratory crackles in both lungs. A chest radiograph and a computed tomography (CT) scan showed discrete ill-defined centrilobular nodules, as well as a patchy ground-glass pattern (figs 2 and 3).

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In the patient’s serum, elevated specific immunoglobulin (Ig) G antibodies were found to 2,4'-toluene diisocyanate (TDI; 42 mg·L⁻¹), 4,4'-methylenediphenyl diisocyanate (MDI; 62 mg·L⁻¹), and 1,6-hexamethylene diisocyanate (HDI; 87 mg·L⁻¹; all ImmunoCAP; Phadia, Freiburg, Germany); the cut-off for increased concentrations using this method was 20 mg·L⁻¹. IgG antibodies to other antigens known to cause HP were not found, e.g., various mould species and acid anhydrides. As there was no contact with birds, IgG antibodies to bird antigens were not determined. IgE antibodies to diisocyanates (again using the ImmunoCAP system) were absent.

Pulmonary function testing showed a mild restrictive pattern (vital capacity (VC) 75.7% predicted, total lung capacity (TLC) 82.0% pred; reference values of European Coal and Steel Community) [5] and a reduction of the diffusing capacity of the lung for carbon monoxide per unit of alveolar volume as assessed by the single breath method (DLCO/VA 46.5% pred) without obstruction. Arterial oxygen tension (PaO₂) fell from 65 to 43 mmHg after a treadmill exercise up to 65 W.

Bronchoalveolar lavage (BAL) showed a total cell count of 2.0 x 10⁶ cells·mL⁻¹ (recovery 130 mL) with 81% lymphocytes, 17% macrophages, 2% neutrophils and a CD4/CD8 ratio of 0.1. The histological examination of transbronchial lung biopsies yielded infiltration of the alveolar septa with lymphocytes, histiocytes and scarce plasma cells, as well as desquamation of pneumocytes and filling of the alveoli by macrophages, but no granuloma formation (data not shown). A diagnosis of subacute occupational HP due to diisocyanates was made.

Follow-up
The patient was treated with prednisolone 1 mg·kg⁻¹ for 4 weeks. After this time, the dose was tapered to 10 mg. This treatment led to significant functional improvement although complete recovery was not achieved (fig. 1). By maintaining treatment with prednisolone (10 mg·day⁻¹) the patient resumed employment, by her own decision, in October 2002. This led to a progressive deterioration in the patient’s health until September 2003 (fig. 1). In July 2003, isocyanate-specific IgG antibodies were found to be slightly higher, similar to the time of diagnosis (TDI: 43 mg·L⁻¹;
MDI: 69 mg·L⁻¹; HDI: 95 mg·L⁻¹). Intensification of therapy, as well as cessation of exposure, resulted in prompt improvement; however, in 2004, after short periods of re-exposure, the patient’s condition worsened. She discontinued working completely in July 2004 and was examined in October 2004 by BGFA (Bochum, Germany).

The patient reported no improvement after cessation of exposure, despite an oral prednisolone dose of 10 mg·day⁻¹ and complained of mild cough with minor mucous phlegm production and shortness of breath after climbing a flight of stairs. However, flu-like symptoms, nightly fever and fatigue had disappeared. Lung function showed mild restriction (VC 95% pred; TLC 84% pred) and DLCO/VA was 35% pred. PaO₂ decreased from 69 to 56 mmHg after exercising for 6 min on a treadmill at 50 W. BAL yielded a total cell count of 2.1 × 10⁵ cells·mL⁻¹ (recovery 80 mL) with 44% lymphocytes, 49% macrophages, 7% granulocytes and a CD4/CD8 ratio of 0.14. Elevated concentrations of specific IgG antibodies to diisocyanates were reproduced by BGFA, although at lower concentrations than the previous examination. The highest IgG antibody concentrations were measured for HDI, as described previously (TDI: 21 mg·L⁻¹; MDI: 49 mg·L⁻¹; HDI: 68 mg·L⁻¹). Total IgG was 12.2 g·L⁻¹ (reference 7–16 g·L⁻¹). Again, IgG concentrations to various moulds and acid anhydrides were not elevated.

IgG inhibition studies using the ImmunoCAP system with HDI, MDI or TDI as solid phase and HDI-human serum albumin (HSA), MDI-HSA and TDI-HSA (1 and 5 mg·mL⁻¹) as inhibitors showed that HDI-HSA was the best inhibitor (table I). Cross-reactivity between all diisocyanates can be assumed. However, somewhat low auto-inhibition, especially in the case of TDI-HSA, shows some limitations, possibly due to different preparation sources of solid and liquid allergens.

A CT scan in October 2004 showed further improvement but there were still ill-defined centrilobular opacities with prevalence in the apical lung fields and patchy ground-glass pattern in the lower parts of both lungs. Discrete differences in bronchial wall thickness persisted (fig. 3). Follow-up examinations until June 2006 showed complete recovery of VC, but a slight reduction of DLCO/VA persisted (fig. 1).

EXPOSURE ASSESSMENT
The shop employed ~60 males and modern spray paint booths were installed. The patient had no access to the booths but had to enter the workshop ~10 times per day for short time-periods. The patient’s office was separated from the workshop by a 3-m-long corridor. The patient complained of an airstream from the workshop to her office. She was obviously at a low-exposure risk as there was no skin contact with isocyanates, and aerosol formation in the patient’s breathing zone was not expected at the locations to which she had access. Thus, inhalational diisocyanate vapor exposure is the most likely exposure source.

The workshop used two-component polyurethane/acrylate-systems for coatings. The hardeners contained 25–50% HDI-homopolymer and up to 1% HDI-monomer according to the material safety data sheets. In addition, MDI-containing 2-pack polyurethane adhesives or patching compounds were used regularly. Air sampling was carried out in June 2004 by the technical staff of the local statutory accident insurance and the quantitative analyses by BGIA (Sankt Augustin, Germany). Sampling of airborne diisocyanates was carried out in the patient’s office, the corridor and in front of the booths while doors were kept closed (18 measurements in total). Both sampling and subsequent quantitative analyses were performed according to German standard procedures for the detection of airborne diisocyanates [6, 7]. Briefly, airborne vapours and aerosols were drawn through a sorption tube filled with glass wool, which was impregnated with N-(4-nitrobenzyl)-n-propylamine (nitroreagent) as a derivatisation reagent. During sample collection, diisocyanates react with nitroreagent to form corresponding soluble urea derivatives. Urea derivatives were eluted from the sampling tubes with dichloromethane immediately after sampling. Quantitative analysis was performed with high-performance liquid chromatography with UV detection. The limits of quantification were 3 and 2 µg·m⁻³ for HDI and MDI, respectively. HDI was not found in any sample, but in one of the samples, a low concentration of MDI was detected (3 µg·m⁻³, sampling in front of one booth). The chromatograms did not indicate any other monomeric or polymeric isocyanates, so the concentration of total reactive isocyanate groups was 1 µg·m⁻³ in front of the spray paint booth, where MDI was detected. The nitrogen, carbon and oxygen (NCO) concentrations in the areas where the patient had access were <1 µg·m⁻³.

DISCUSSION
HP in this patient was documented by a typical history, a restrictive ventilation pattern, compatible radiographs/high-resolution CT, a typical BAL differential cell count with a low...
CD4/CD8 ratio, and elevated diisocyanate-specific IgG antibody concentrations. A transbronchial lung biopsy is compatible with the diagnosis of sub-acute HP, which seems to be an extremely rare disease, but is possibly often misdiagnosed [8].

The patient had been exposed to diisocyanates, known to cause HP since the 1970s [9]. A relationship between HP and the patient’s occupation was demonstrated by high concentrations of diisocyanate-specific IgG antibodies in her serum and a clinical course (symptoms, diisocyanate-specific IgG antibody concentrations, radiographs/high-resolution CT and lung function) that was closely linked to exposure. Nonoccupational exposure to diisocyanates was denied. The patient did not recover completely after cessation of exposure. This does not argue against the diagnosis of HP as it is known from the literature that the outcome of sub-acute or chronic forms of HP is poor [10, 11]. Thus, there is virtually no doubt about a diagnosis of occupational HP, which was categorised as sub-acute due to the available information.

Up to approximately four-fold elevated diisocyanate-specific IgG antibody concentrations were documented by two independent laboratories with the same method (Institute of Lung Diseases and Allergy, Bonn, Germany and BGFA). A cut-off for increased concentrations of 20 mg·L⁻¹, as recommended by the manufacturer, is used by both laboratories. It has been corroborated by the current authors in a small series of nonexposed control subjects (R. Merget, personal communication).

To the present authors’ knowledge, no case-control studies have been performed that allowed an estimate of the importance of cross-reactive IgG antibodies to different diisocyanates in HP, while cross-reactions between isocyanates have been reported in isocyanate asthma [12–14]. One case report of a car painter with HP described the existence of IgG antibodies to all three diisocyanates [15], whereas in another HP case IgG antibodies against polymeric MDI did not cross-react with TDI and HDI [16]. The exposure in the present case was mainly to HDI, but exposure to MDI also occurred. Exposure to TDI could not be documented at the patient’s workplace. IgG inhibition experiments corroborated the interpretation that HDI is the primary sensitiser, although some cross-reactivity between diisocyanates was present. Relevant nonspecific binding to IgG can be excluded. Weak nonspecific binding to IgG in 12 out of 40 diisocyanate-exposed subjects with sensitisation to diisocyanates in the IgE system has been described previously [17]. The present case demonstrates that the measurement of diisocyanate-specific IgG antibodies is an appropriate tool for diagnosing HP.

It is known that HDI is dominant in frequency and exposure level in the car painting industry [18]. This assumption is corroborated by the inhibition experiments and the patient’s IgG antibody response, which showed higher concentrations to HDI than to TDI and MDI. The origin of elevated MDI concentrations in one air sample could not be elucidated but may be a coating compound containing MDI that was used in the workshop.

Measurements of monomer concentrations in the air yielded detectable isocyanate concentrations in only a single sample in front of one booth, which was far below current exposure limits, e.g. 34 μg·m⁻³ time-weighted average for HDI monomers [19]. Recently, a high number of isocyanate measurements were performed in 24 car body repair shops with the inclusion of monomers, oligomers and thermal degradation products [18]. In the present study, 28 measurements were also carried out in the offices of car body repair shops. Concerning HDI, 10 measurements were above the level of detection with a median concentration (range) of 0.04 (0.001–0.13) μg·m⁻³ NCO. In total, 16 measurements were carried out near drying areas; these yielded 12 samples above the level of detection with a median concentration (range) of 0.49 (0.01–2.67) μg·m⁻³ NCO. At both locations the concentrations were much lower than concentrations near the spray painting. Out of four measurements, three were above the level of detection with a median concentration (range) of 10.47 (0.07–10.48) μg·m⁻³ NCO. These results are plausible and indicate that the patient’s exposure was far below current exposure limits, which were set, for example, in Sweden or the UK at 20 μg·m⁻³ time-weighted average (as NCO groups).

The present case indicates that sub-acute or chronic occupational hypersensitivity pneumonitis may be induced by low isocyanate levels. This has consequences both for prevention and diagnosis [20]. There is also an impact on the diagnosis of interstitial lung diseases beyond hypersensitivity pneumonitis because a chronic clinical course in subjects without known occupational risk may obscure the correct diagnosis.

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