

## Short communication

# Occupational asthma caused by exposure to cyanoacrylate

**Background:** Exposure to acrylates may give rise to rhinitis and asthma in both industrial and domestic environments. The mechanisms underlying these respiratory conditions caused by acrylates remain largely unknown.

**Methods:** We studied two assembly operators exposed to cyanoacrylate glue who developed rhinitis and asthma symptoms. The causal relationship of these symptoms to cyanoacrylate glue exposure was investigated by serial peak expiratory flow (PEF) monitoring at work and off work. Moreover, inhalation testing was performed by asking the patients to mimic exposure at work with the cyanoacrylate glue in a 7-m<sup>3</sup> challenge chamber.

**Results:** Serial PEF monitoring at work and away from work was consistent with occupational asthma in both patients. The methacholine inhalation test was negative in patient 1 (off work) and showed bronchial hyperresponsiveness in patient 2. After 20-min exposure to cyanoacrylate, the patients had late and progressive asthmatic reactions, respectively, and the methacholine test became positive in patient 1. Induced-sputum samples obtained 3 and 24 h after the cyanoacrylate challenge showed a marked increase in sputum eosinophils.

**Conclusions:** Exposure to cyanoacrylate in these patients provoked not only variable airflow limitation and bronchial hyperresponsiveness, but also pronounced eosinophilia in sputum.

S. Quirce<sup>1</sup>, M. L. Baeza<sup>2</sup>,  
P. Tornero<sup>2</sup>, A. Blasco<sup>3</sup>,  
R. Barranco<sup>2</sup>, J. Sastre<sup>1</sup>

<sup>1</sup>Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid; <sup>2</sup>Hospital Gregorio Marañón, Madrid;

<sup>3</sup>Hospital San Millán y San Pedro, Logroño, Spain

Key words: cyanoacrylate; eosinophils; induced sputum; occupational asthma.

Dr Santiago Quirce  
Fundación Jiménez Díaz  
Servicio de Alergia  
Avda. Reyes Católicos, 2  
28040 Madrid  
Spain

Accepted for publication 11 December 2000

Acrylic compounds are extensively used in the manufacture of products such as adhesives, thermoplastics and acrylic resins, solvents, paints, coatings, printing inks, and soft contact lenses, and in the embedding of histologic preparations (1, 2). Cyanoacrylate-based glues provide a high bond strength between a variety of materials and are suitable for surgical use as a tissue adhesive and for home repairs and hobbies ("super-glues" and instant glues). Methacrylates serve as bases for acrylic resins, which are used in the production of prostheses, adhesives, and fillers in dental and orthopedic procedures.

Acrylic monomers have been shown to be irritant to the eyes and mucous membranes (2), and are well-known contact allergens (3, 4). In recent years, it has been shown that different acrylates may give rise to rhinitis and asthma in both industrial and domestic environments (2, 5–14). However, the mechanisms underlying these respiratory conditions remain largely unknown.

## Material and methods

### Skin tests

Skin prick tests were performed with a battery of common inhalant allergens and with natural latex extract (ALK-Abelló, Madrid,

Spain). Histamine phosphate at 10 mg/ml and normal saline were used as positive and negative controls, respectively. A wheal with a mean diameter of 3 mm or greater with erythema occurring 15 min after testing, compared with the saline control, was defined as a positive reaction.

### Peak expiratory flow monitoring

Serial determinations of peak expiratory flow (PEF) with a Mini-Wright peak flow meter (Clement Clarke Ltd, London, UK) were performed by the patient at 4-h intervals during waking hours at work and away from work for at least 4 weeks. The maximum and minimum values were kept for analysis of daily variability. Records with a diurnal variation of 20% or greater were considered to be significant for daily variability as described (15).

### Methacholine inhalation test

This test was performed according to Cockcroft et al. (16) with some modifications. The aerosolized particles were generated by a continuous pressurized nebulizer model De Vilbiss 646 (De Vilbiss Co., Somerset, PA, USA) with an output of 0.28 ml/min. The result was expressed as the provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 s (PC<sub>20</sub>). According to our laboratory standards, a PC<sub>20</sub> of >16 mg/ml is considered to be within normal limits, and PC<sub>20</sub> values of 16–1 mg/ml, 1–0.125 mg/ml, and <0.125 mg/ml indicate mild, moderate, and severe bronchial hyperresponsiveness, respectively.

### Specific bronchial challenge test

The inhalation challenge test was performed by asking the patient to

mimic exposure at work, using the cyanoacrylate-based glue in a 7-m<sup>3</sup> challenge chamber, as previously described (2, 5, 12). The patient handled the cyanoacrylate glue as follows: the glue, contained in an opaque dispenser, was spread on a piece of cardboard for increasing periods of 5, 10, and 20 min. On a control day, the patient was exposed to nonacrylate glue (Sader®, Krafft SA, Andoain, Spain) for 20 min. On the second day, the patient was exposed to cyanoacrylate glue for progressively increasing periods of time, and FEV<sub>1</sub> and FVC were measured at 5, 10, and 20 min after exposure. The clinical symptoms and lung auscultation were recorded as well. The patient took no medications for at least 3 days before challenge. The temperature in the challenge chamber was 24°C, and the humidity was 32%. The inhalation challenge test was discontinued when there was a fall in FEV<sub>1</sub> of 20% or greater from baseline value or when the longest exposure time was completed. At the end of the inhalation challenge test, spirometry was performed at 30, 40, 50, and 60 min, then hourly for 9 h after challenge, and again the following day. From that moment, PEF and FEV<sub>1</sub> measurements were done hourly with a computerized flowmeter (VM Plus, Clement Clarke Ltd, Harlow, UK) for 24 h after challenge, respecting sleeping time. A fall in FEV<sub>1</sub> of 20% or more from baseline within 60 min of challenge was considered a positive immediate reaction, and a similar fall at 2–24 h after challenge was considered a positive late reaction if no change was observed during the control day.

#### Sputum induction and processing

Induction of sputum was performed as described by Pin et al. (17). Briefly, PEF was measured before and after salbutamol inhalation (200 µg) to prevent airway constriction. Hypertonic saline was then nebulized with an ultrasonic nebulizer (Ne-U10B, Omron Corp., Japan) for up to 21 min. The concentration of saline was 3%, followed by 4%, followed by 5% each for 7 min. Subjects were encouraged to cough throughout the procedure, and they regularly interrupted inhalation of hypertonic saline solution to expectorate sputum into a Petri dish. Sputum samples were then processed and homogenized with the addition of 20 ml of trypsin 0.001 mg/ml (Merck, Darmstadt, Germany) in normal saline (18). The samples were then incubated at 60°C for 30 min and centrifuged at 2000 rpm for 10 min. The cell pellets were resuspended in saline solution and stained with the Papanicolaou and Giemsa methods for differential cell counts. Two investigators counted at least 200 nonsquamous cells on each sputum slide.

## Results

### Patient 1

A 46-year-old woman, an ex-smoker, was employed for 1 year as an assembly operator in a factory making weather strips for cars. At work, she used glue containing ethyl cyanoacrylate (Sicomet 8300®, Henkel, Hanover, Germany), which she applied at the end of the rubber strips. About 3 months after the start of employment, she developed nasal stuffiness, rhinorrhea, and sneezing, and 1 month later she noticed episodes of chest tightness, dry cough, wheezing and shortness of breath. Symptoms commenced at the end of the work shift and often worsened at home and caused nocturnal awakenings. Her symptoms were progressively severe and then she took sick leave, during which she completely recovered. When evaluated in our clinic, she had been away from work for 20 days and she was symptom-free and taking no asthma medication.

The absolute eosinophil count in peripheral blood was 350 eosinophils/mm<sup>3</sup>. The serum total IgE level was 17 kU/l. Skin prick tests to common aeroallergens and latex were negative. Chest radiography was normal. Spirometry revealed a FVC of 3.47 l (90% predicted), FEV<sub>1</sub> of 2.95 l (100% predicted), and FEV<sub>1</sub>/FVC of 85%. The methacholine inhalation test was negative (PC<sub>20</sub> > 16 mg/ml). Serial monitoring of PEF showed about 20% daily variability during working days and less than 10% when she was off work. She underwent a specific inhalation challenge test and after 20-min exposure to cyanoacrylate glue for 20 min, both nasal symptoms and a late asthmatic response were observed (Fig. 1). The methacholine inhalation test became positive (PC<sub>20</sub> = 1 mg/ml) 24 h after challenge with cyanoacrylate. Eosinophil counts in sputum samples obtained before and after the cyanoacrylate challenge are shown in Table 1. No asthmatic reaction occurred after inhalation testing with nonacrylate glue on a separate control day.

### Patient 2

A 24-year-old woman, a nonsmoker, worked as an assembly operator in a rubber-processing plant. She used daily ethyl cyanoacrylate glue (Sicomet 8300) for the assembly of weather strips for cars. Eighteen months after starting this work, she suffered from nasal and conjunctival itching, nasal stuffiness, rhinorrhea, and sneezing. Three months later, she developed dry cough, shortness of breath, and wheezing that were aggravated in the evening and at night. Symptoms became progressively worse during the working week, improved at weekends, and disappeared during holidays. Although she had been put on fluticasone 250 µg b.i.d., she used this medication very erratically, relying on inhaled salbutamol as required for asthma control. The eosinophil count in peripheral blood was 329 eosinophils/mm<sup>3</sup>. Total serum IgE was 42.5 kU/l. Chest radiography was normal. Skin tests to common aeroallergens and latex were negative. Spirometry

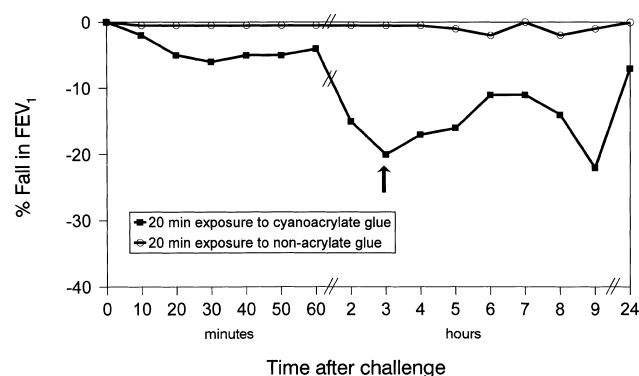


Figure 1. Specific inhalation challenge to nonacrylate (control) and cyanoacrylate glue, showing late asthmatic reaction. Arrow indicates salbutamol inhalation (200 µg).

Table 1. Pulmonary function parameters and eosinophil counts in sputum before and 3 and 24 h after bronchial provocation test (BPT) to cyanoacrylate

|                                       | Baseline | 3 h after BPT | 24 h after BPT |
|---------------------------------------|----------|---------------|----------------|
| FEV <sub>1</sub> (l)                  |          |               |                |
| Patient 1                             | 2.95     | 2.36          | 2.74           |
| Patient 2                             | 3.26     | 2.67          | 3.22           |
| PC <sub>20</sub> methacholine (mg/ml) |          |               |                |
| Patient 1                             | > 16     | ND            | 1              |
| Patient 2                             | 0.27     | ND            | ND             |
| Sputum eosinophils (%)                |          |               |                |
| Patient 1                             | 10%      | 80%           | 90%            |
| Patient 2                             | 30%      | 70%           | 70%            |

ND: not done.

revealed FVC of 4.09 l (104% predicted), FEV<sub>1</sub> of 3.26 l (97% predicted), and FEV<sub>1</sub>/FVC of 80%. The methacholine inhalation test demonstrated bronchial hyperresponsiveness (PC<sub>20</sub>=0.27 mg/ml). Serial recordings of PEF showed 20–28% daily variability during a 15-day working period and 0–10% variation during 1 month away from work. After a 20-min exposure to cyanoacrylate glue, she developed rhinitis and an atypical bronchial reaction of the progressive type (19) with maximum fall in FEV<sub>1</sub> of 50% 4 h after exposure (Fig. 2). Inhaled salbutamol and oral methylprednisolone were administered, leading to functional and clinical recovery within a few hours. Eosinophil counts in sputum samples at baseline and after the cyanoacrylate inhalation challenge are shown in Table 1. No asthmatic reaction occurred after testing with nonacrylate glue on a separate control day. She was relocated to a different area in the company and remained symptom free after that. Two asthmatic patients were challenged with the same cyanoacrylate glue for 20 min, and no reaction was observed.

## Discussion

Cyanoacrylate glues are very volatile and chemically reactive compounds (1). They are widely used in industry and in the home because of their easy handling and great sticking power due to anionic polymerization. Acrylate monomers are irritants to the mucous membranes. Maintaining a high level of humidity in the workplace can reduce the atmospheric concentration of cyanoacrylate monomers, because they react with water vapor in the air, forming less volatile polymers (3, 5).

Since 1985, several cases of asthma caused by acrylates, mainly affecting dental personnel and adhesive handlers, have been reported (2, 5–14). As there is a latency period between the onset of exposure to acrylates and the development of asthma symptoms, a “sensitizing” mechanism is presumed (2, 5, 9). Moreover, isolated late, dual, or atypical asthmatic reactions have been observed after specific inhalation

challenge in most cases. However, the mechanism of sensitization is currently unknown. There is no evidence of a specific IgE-mediated reaction to acrylates. Due to the physical properties of cyanoacrylate, it is not possible to perform prick tests or specific IgE measurements with the compound itself (13). Prick tests with human serum albumin (HSA) conjugated with different acrylates have been unsuccessful, but it is not clear whether the HSA-acrylate conjugates represent true allergens (2, 9). However, since most cases of asthma caused by acrylates have shown late asthmatic reactions, the negativity of skin prick test responses is likely to be due to the fact that acrylates induce asthma through an IgE-independent mechanism.

The patients herein reported developed rhinitis and late or progressive asthmatic reactions, respectively, after cyanoacrylate inhalation challenge. Although we followed a “workplace-type” challenge protocol with cyanoacrylate glue, which has been safely used by other investigators (2, 5, 12), and which was well tolerated by patient 1, it elicited a severe atypical asthmatic response in patient 2. Thus, we think that exposure to cyanoacrylate in patients with enhanced nonspecific bronchial hyperresponsiveness should be limited to a maximum of 1–5 min on the first day of exposure, as late asthmatic reactions are common with low-molecular-weight agents, and their severity is unpredictable. On the other hand, a 2-h exposure period to acrylates may be necessary to obtain a positive asthmatic reaction in some patients (14).

Interestingly, exposure to cyanoacrylate was able to induce the development of nonspecific bronchial hyperresponsiveness in patient 1. This postchallenge increase in bronchial hyperresponsiveness is useful to distinguish an asthmatic reaction due to specific mechanisms from bronchoconstriction triggered by an irritant effect. Moreover, induced sputum can be a useful, noninvasive, tool to support the evidence related to the occurrence of an asthmatic reaction following

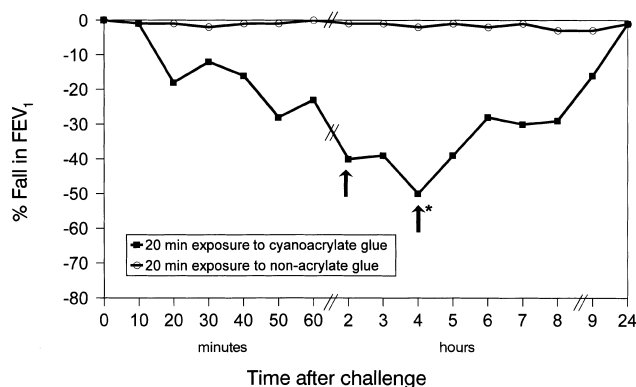


Figure 2. Specific inhalation challenge to nonacrylate (control) and cyanoacrylate glue, showing atypical asthmatic reaction of progressive type. Arrows indicate salbutamol inhalation (400 µg) and (\*) oral methylprednisolone (32 mg).

specific inhalation challenge and to distinguish true occupational asthma from aggravation of asthma due to irritants (20). Recently, Lemièrre et al. (21) reported a subject who experienced a late asthmatic reaction after exposure to diacrylates associated with a clear increase in sputum eosinophils even though bronchial hyperresponsiveness before and after exposure was absent. Moreover, acrylates have been found to cause eosinophilic bronchitis without asthma (22).

To the best of our knowledge, this is the first study to demonstrate that exposure to cyanoacrylate can provoke the development of occupational asthma

associated with bronchial hyperresponsiveness and intense eosinophilic airway inflammation. Although the mechanisms of asthma and other respiratory conditions caused by acrylates remain unknown, they seem to be associated with a strong eosinophil-recruiting stimulus.

### Acknowledgment

We thank Dr Francisca Rivas for kindly performing the cell counts in sputum.

### References

1. COOVER HW, MCINTIRE JM. Cyanoacrylate adhesives. In: SKEIST I, editor. Handbook of adhesives. New York: Rheinhold, 1977:569–580.
2. PIIRILÄ P, KANERVA L, KESKINEN H, et al. Occupational respiratory hypersensitivity caused by preparations containing acrylates in dental personnel. *Clin Exp Allergy* 1998;**28**:1404–1411.
3. CALNAN CD. Cyanoacrylate dermatitis. *Contact Dermatitis* 1979;**5**:165–167.
4. CONDE-SALAZAR L, ROJO S, GUIMARAENS D. Occupational allergic contact dermatitis from cyanoacrylate. *Am J Contact Dermatitis* 1998;**9**:188–189.
5. LOZEWICZ S, DAVISON AG, HOPKIRK A, et al. Occupational asthma due to methyl methacrylate and cyanoacrylates. *Thorax* 1985;**40**:836–839.
6. KOPP SK, MCKAY RT, MOLLER DR, CASSEY K, BROOKS SM. Asthma and rhinitis due to ethyl cyanoacrylate instant glue. *Ann Intern Med* 1985;**102**:613–615.
7. PICKERING CA, BAINBRIDGE D, BIRTWHISTLE IH, GRIFFITHS DL. Occupational asthma due to methacrylate in an orthopaedic theatre sister. *Lancet* 1986;**292**:1362–1363.
8. NAZAWA T. Occupational asthma due to alkyl cyanoacrylate. *J Occup Med* 1990;**32**:709–710.
9. SAVONIUS B, KESKINEN H, TUPPURAINEN M, KANERVA L. Occupational respiratory disease caused by acrylates. *Clin Exp Allergy* 1993;**23**:416–424.
10. THOMSEN GF. Occupational asthma induced by cyanoacrylate glue. *Ugeskr Laeger* 1994;**156**:5131–5132.
11. CHAN CG, CHEONG TH, LEE HS, WANG YT, POH SC. Case of occupational asthma due to glue containing cyanoacrylate. *Ann Acad Med Singapore* 1994;**23**:731–733.
12. GARCÉS MM, BLANCO JG, JUSTE S, et al. Asma bronquial ocupacional inducido por cianoacrilato. *Rev Esp Alergol Immunol Clin* 1995;**10**:21–24.
13. KOPFERSCHMIT-KUBLER MC, STENGER R, BLAUMEISER M, et al. Asthma, rhinitis and urticaria following occupational exposure to cyanoacrylate glues. *Rev Mal Respir* 1996;**13**:305–307.
14. WEYENS K, CARTIER A, LEMIÈRE C, MALO JL. Occupational asthma to diacrylate. *Allergy* 1999;**55**:289–290.
15. LISS GM, TARLO SM. Peak expiratory flow rates in possible occupational asthma. *Chest* 1991;**100**:63–69.
16. COCKROFT DW, KILLIAN DN, MELLON JJA, HARGREAVE FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;**7**:235–243.
17. PIN I, FREITAG AP, O'BYRNE P, et al. Changes in the cellular profile of induced sputum after allergen-induced asthmatic response. *Am Rev Respir Dis* 1992;**145**:1265–1269.
18. TOCKMAN MS, QIAO Y, LI L, et al. Safe preparation of sputum cells from mucoid glycoprotein. *Acta Cytol* 1995;**39**:1128–1136.
19. PERRIN B, CARTIER A, GHEZZO H, et al. Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol* 1991;**87**:630–639.
20. LEMIÈRE C, PIZZICHINI MMM, BALKISSOON R, et al. Diagnosing occupational asthma: use of induced sputum. *Eur Respir J* 1999;**13**:482–488.
21. LEMIÈRE C, WEYJENS K, CARTIER A, MALO JL. Late asthmatic response with airway inflammation but without bronchial hyperresponsiveness. *Clin Exp Allergy* 2000;**30**:415–417.
22. LEMIÈRE C, EFTHIMIADIS MLT, HARGREAVE FE. Occupational eosinophilic bronchitis without asthma: an unknown occupational airway disease. *J Allergy Clin Immunol* 1997;**100**:852–853.