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Case report

Sensitization to triglycidylisocyanurate (TGIC) with cutaneous and respiratory manifestations

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Key words: allergic contact dermatitis; bronchial provocation testing; occupational asthma; paints; resins; self-measured FEV₁; triglycidylisocyanurate (TGIC).

The case is presented of a man with allergic contact dermatitis and occupational asthma due to triglycidylisocyanurate (TGIC), which is used as a hardener in thermosetting powder paint. The contact dermatitis was confirmed by patch testing (TGIC 0.5% and 5% in petrolatum), and the occupational asthma was confirmed by bronchial provocation testing: two challenges to an aerosol of lactose containing TGIC (0.05% and 0.1%, w/w, each for 0.5+1+2+4 min) led to a maximal decrease in FEV₁ of 22% and 31% after 6 and 4 h, respectively. Skin prick tests with unconjugated TGIC were possibly positive. This case confirms that exposure to TGIC in powder paints may cause not only contact dermatitis, but also occupational asthma.

Triglycidylisocyanurate (TGIC) is a hardener in thermosetting polyester powder coatings and is known to be a contact sensitizer in occupationally exposed subjects (1–7). Since such powder paints are applied by (electrostatic) spraying techniques, occupational asthma due to inhalation might be expected as well.

We here present a well-documented case of occupationally induced allergic contact dermatitis and asthma.

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Case report

A previously healthy, nonsmoking, 38-year-old man without pre-existing atopic disease first presented in June–July 1996 with cutaneous and respiratory complaints that had started 8 months previously. For 3 years, he had been

employed in the air-spraying of metal frames with polyester powder pigments. He wore a protective mask, but no gloves. Yearly medical examinations, which included spirometry, had always been unremarkable. Respiratory symptoms (rhinitis, cough, dyspnea, and wheezing) had appeared shortly after the beginning of the cutaneous signs, which had commenced in the elbow and knee folds, and later spread to other body areas. There was a clear association with his occupational activities, since his symptoms decreased during weekends and cleared completely on vacation, particularly during a period of sick leave for orthopedic surgery in February 1996. Systemic symptoms or fever were not reported.

Dermatologic assessment

Clinical examination revealed erythematous, papular, and plaque-like lesions on the medial and flexural sites of the arms, and extensor parts of the legs, as well as the axillae and the upper part of the back. Patchy, erythematous, infiltrated, and slightly scaling lesions were also present on the face, mainly on the forehead and in the perioral area. There were no lesions on the hands. At a later visit, he also presented eczema on the eyelids, as well as the upper lip and neck. Local application of corticosteroids had brought partial relief of the symptoms, and systemic administration completely cleared the lesions, but they reappeared as soon as the treatment was discontinued.

The patient was patch tested on several occasions (August, October, and December 1996), according to international recommendations (8), with the standard series; azo dyes; and the epoxy resin series, including diaminodiphenylmethane (0.5% pet), hydroxyethylmethacrylate (2% pet), and TGIC (0.5 and 5% pet), as well as with two samples of the pigment powders he worked with. No immediate readings were performed. Positive tests were obtained to diaminodiphenylmethane (++) after 2 and 4 days), to TGIC (++ on days 2 and 3 with the 5%, and on day 3 with the 0.5% dilution), and to one of the pigment powders (+ on day 3, tested as is). According to material safety data sheets obtained from the manufacturer, the product contained polyester resin, TGIC (in a concentration of 1–7%, w/w), mineral fillers, and pigments.

Respiratory assessment

When the patient was first seen in the pneumology clinic in June and July 1996, the possibility of occupational asthma was considered but not immediately recognized, mainly

because there was little objective evidence of asthma; indeed, pulmonary function tests were perfectly normal, including a histamine test (9), which gave a PC₂₀ of >8 mg/ml. However, the latter was carried out during the patient's summer vacation. The only laboratory abnormalities at the time were elevated blood eosinophilia (23% or 3100/μl) and serum IgE (688 IU/ml), which were attributed to his supposed atopic dermatitis. RASTs were negative for common environmental allergens (*Dermatophagoides pteronyssinus*, dog, birch, *Phleum pratense*, *Plantago lanceolata*, and *Aspergillus fumigatus*), and there were no precipitins against *A. fumigatus*. Radiography of the chest and sinuses was normal.

However, when he was seen again in November 1996, the clinical history had become much more suggestive of occupational asthma. This was confirmed by sequential self-measurements of pulmonary function with an electronic device (Spirobank[®], MIR, Rome, Italy), which showed suggestive, though not entirely clear-cut work-related changes in FEV₁ (Fig. 1) and PEF (not shown). Values of histamine PC₂₀ were 0.05 and 0.30 mg/ml on 13 and 24 December 1996, respectively.

To confirm that the cause of the occupational asthma was TGIC, specific bronchial provocation tests were carried out in January 1997, according to existing recommendations (10). TGIC (Araldite PT810, batch 504574, dust-free prills, approximate purity of TGIC 90%, received from Dr A.E. Smith, then at CIBA, and now at Novartis, Basel, Switzerland) was pulverized with a mortar. Dust was aerosolized in a plexiglass cylinder built as described by Weyel et al. (11), with additional use of compressed air, and was inhaled, by mouth, through a Hans-Rudolph valve connected to the cylinder, via a 25-cm-long flexible tube. A control test using an aerosol of lactose powder for a total of 16 min did not lead to any respiratory symptom or decrease in ventilatory function (Fig. 2, top panel). With the agreement of the patient, the lactose contained a small amount of an unrelated agent which had caused an epidemic of occupational asthma in another factory. The following day, the patient was exposed to an aerosol of lactose containing TGIC (50 mg TGIC in 100 g lactose) for a total of 7.5 min. The exposure was well tolerated but was followed, 3 h later, by a progressive decrease in ventilatory function to a maximum of –22% in FEV₁ at 6 h, with slight cough and dyspnea, but no wheezing, and then a spontaneous recovery (Fig. 2, middle panel). Although this test could be considered positive, the observed pattern of the decrease (a so-called early-late reaction [12]) was not typical; therefore, it was decided, with the patient's approval, to repeat the test on the

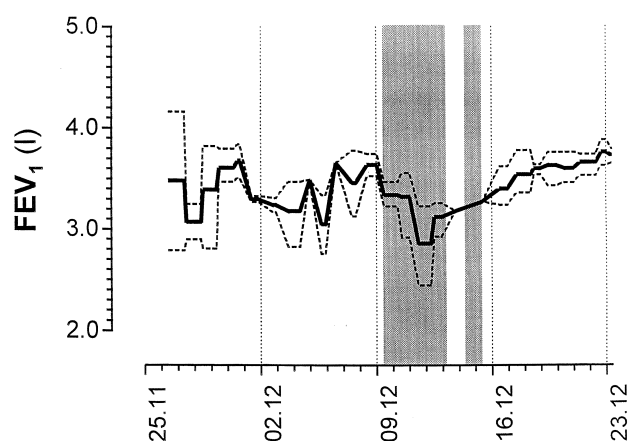


Figure 1. Self-measured FEV₁ by portable electronic spirometer (Spirobank®) as function of time (numbers on horizontal axis are dates, expressed as day and month in 1996). Patient was instructed to perform forced expiratory maneuvers (two to three acceptable blows each time, with best curve being stored) three to four times per day (on some days, only one measurement was made). Results are depicted according to Burge (18), with thick full line being daily mean value (between 10 a.m. and 10 a.m.) and thin interrupted lines daily minimum and maximum values. Shaded areas correspond to days during which patient worked in powder-spraying department. Previously, he had worked elsewhere in plant; after that time, he was at home.

following day. The second test was done as the first one, but with twice the concentration (100 mg TGIC in 100 g lactose), and it was now very clearly positive with a maximal decrease in FEV₁ of -31% and wheezing at auscultation, 4 h after exposure (Fig. 2, lower panel). There was a strong, but temporary response to salbutamol, but the patient experienced cough, wheezing, and dyspnea, as well as itching during the following night. The next morning, the FEV₁ was still decreased and the patient was given a short course of methylprednisolone. There were no changes in blood leukocytosis or eosinophils 6 h after the TGIC tests (6.8% and 6.1% eosinophils), but on both mornings after these tests, there was an increase in blood eosinophils (12.8% on both mornings after the TGIC tests, vs 7.7% on the morning after the lactose test). A week later his lung function was normal.

The patient was moved to another job within the same hall, but about 50 m away from the spraying cabin. Four months later, he was asymptomatic but his histamine PC₂₀ was still low at 0.27 mg/ml. When last seen (January 1999), he was working mostly outdoors as a forklift-driver and had not had any serious recurrence of dermal or respiratory symptoms, although he sometimes had slight respiratory symptoms when he entered the plant. His ventilatory function had not changed, but his histamine PC₂₀ had improved (1.4 mg/ml). Skin prick tests were then also

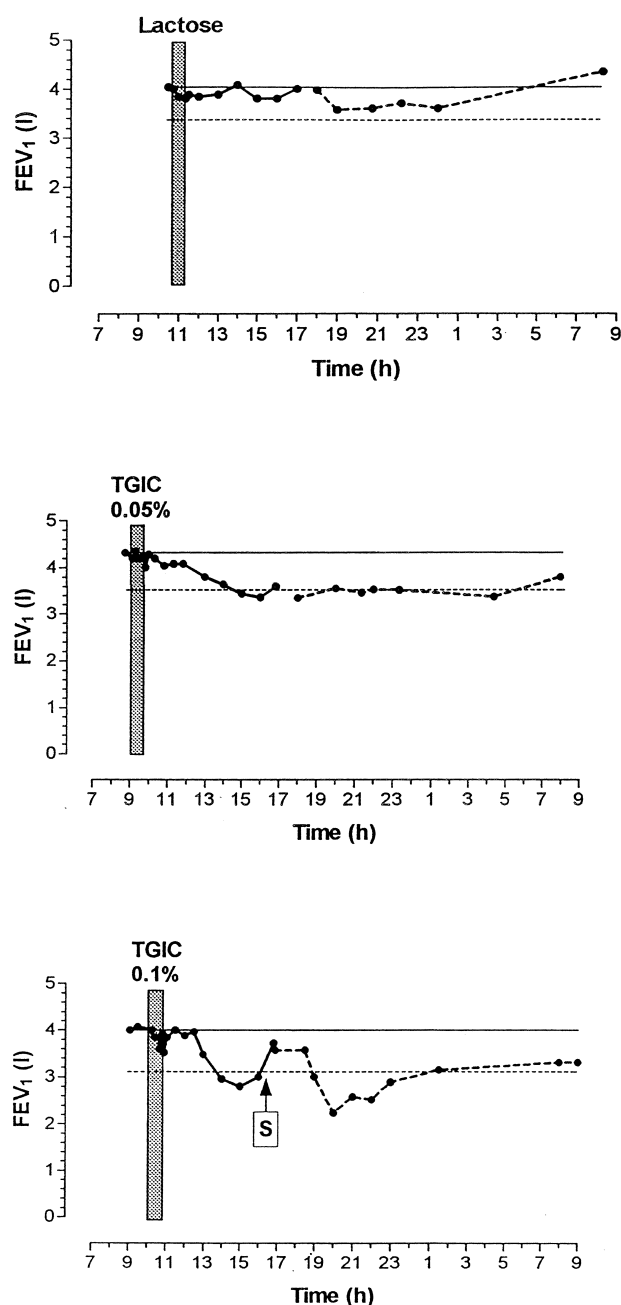


Figure 2. Specific bronchial provocation tests with lactose (top panel), TGIC 50 mg/100 g lactose (0.05%, middle panel), and TGIC 100 mg/100 g lactose (0.1%, bottom panel) on three successive days. Values on horizontal axis are absolute time of day. Exposure (shaded bars) was carried out by having subject inhale aerosol, produced by purpose-built apparatus, for periods of 1, 5, and 10 min (lactose) or 0.5, 1, 2, and 4 min (TGIC), each period being separated by 10 min for measurement of spirometry at 1 and 10 min. Data points linked by interrupted line (after 1700) are self-measured values obtained with electronic spirometer (Spirobank®) and have been multiplied by 1.15, because of systematic underestimation of self-measured FEV₁ compared to concomitant measurements made with pneumotachograph (based on 21 pairs of measurements). Horizontal lines represent day's initial value (full line) and 80% of that initial value (dotted line). S indicates administration of two salbutamol puffs.

performed with TGIC dissolved (and sonicated) in either NaCl 0.9% or dimethylsulfoxide (DMSO). The patient exhibited considerable dermographism. The responses to TGIC appeared positive; i.e., they showed a wheal similar to that obtained with histamine, when testing 1-week-old solutions (0.01%, w/v) of TGIC from the same batch as the one used for the bronchial challenge. However, no such reactions were seen with fresh solutions of that same TGIC or when tests were made with either 1-week-old or fresh solutions of TGIC purchased from Aldrich (all tested up to 1%, w/v). None of the solutions were positive when tested in another subject, and some were inconsistently positive in another subject.

Discussion

The positive patch test and specific bronchial provocation test, together with the occupational and clinical data, argue for a concomitant allergic contact dermatitis and occupational asthma as a result of sensitization to TGIC.

The reaction to TGIC was considered relevant to the patient's condition. The relevance of the positive test to diaminodiphenylmethane, however, could not be determined, because it did not appear to be present in the materials to which the patient was exposed and because it is not chemically related to TGIC.

With regard to the bronchial provocation test, the clear-cut response found here adds credence to the findings recently published by Piirilä et al. (13), who described the first case of TGIC-induced occupational asthma. Our confirmatory data are important because Piirilä et al. (13) used higher concentrations of TGIC and longer challenge

durations. Moreover, although the response patterns observed by these authors were convincing, the decreases in ventilatory parameters found in their patient did not generally attain the conventional 20% required for a positive response, except for a single decrease in FEV₁ of 23% at 11 h after one of the challenges.

The mechanisms of the respiratory sensitization in our patient are not known, and we have no immunologic evidence of specific IgE-mediated reactions. The responses to the skin prick tests with unconjugated TGIC were inconsistent and not readily interpretable at this stage. It is noteworthy that both our patient and that of Piirilä et al. (13) had a high total serum IgE, but no personal history of atopy. However, the occurrence of asthma does not necessarily imply that the mechanisms involved are IgE-mediated; cell-mediated immune reactions may also play a role in asthma caused by low-molecular-weight compounds (14).

It is remarkable that, according to the manufacturer's information (A.E. Smith, personal communication), the sensitization potential of TGIC in experimental animals was not pronounced (and even below the threshold used in the EU for classification as a skin sensitizer). Moreover, a local lymph-node assay, carried out according to Ikarashi et al. (15) in BALB/c mice, remained negative, at least up to a tested concentration of 5.0% (16). This suggests that considerable problems still remain in the field of the identification of potential respiratory sensitizers (17). In any event, we believe that the occurrence of TGIC-induced asthma indicates that agents that have demonstrated sensitization potential for the skin, either in human subjects or in animal assays, should, as a rule and until proven otherwise, also be considered potential causes of asthma if they are likely to be inhaled as vapors or aerosols.

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