

Phthalic anhydride asthma

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Summary

A patient with occupational asthma caused by phthalic anhydride is described. Inhalation challenges under laboratory control produced immediate and delayed asthmatic responses. Repeat exposure to phthalic anhydride after treatment with cromolyn sodium showed inhibition of the late but not the early bronchoconstrictive, asthmatic response.

Introduction

Recently it has become apparent that phthalic acid esters are widely dispersed in the environment. The implications for health are unclear. Phthalates are used in the manufacture of plastics and are therefore in virtually every major product category (Graham, 1973). The annual production of various phthalic diesters approximates 10^6 lb and, while human exposures would appear to be most significant in occupations where phthalates are used, there is evidence for a considerable general atmospheric exposure (Tepper, 1973). It is generally felt that these materials are non-toxic (Tepper, 1973; Hamilton & Hardy, 1974), but there is a Russian report of polyneuritis in workers exposed to phthalate esters (Tepper, 1973) and also reported disturbances of reproduction and growth of aquatic species in water containing phthalic acid esters at concentrations of approximately $3 \mu\text{g/l}$. This report confirms the association of asthma with phthalic anhydride previously reported by Maccia (Maccia *et al.*, 1976).

Case report

The patient was a 41-year-old man employed by a tyre and rubber manufacturer for 19 years. His health had been excellent. Sixteen months before examination he developed episodic dyspnoea accompanied by cough which was worse at night. He had been exposed to phthalic anhydride for 19 years but during these 16 months he noted that acute exposure at work caused immediate chest 'tightness' and dyspnoea. The symptoms disappeared as work progressed but recurred, more severely, during the evening. A 1 week vacation completely relieved the increasing frequency of episodes of dyspnoea. On the day after returning to work, the symptoms recurred. The patient

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was a non-smoker. He had had allergic rhinitis since childhood, not requiring continuous medical care. There was no other history of chest disease or asthma. Because of interference with his work, he came to the Allergy Clinic at University Hospitals.

Physical examination was completely normal. The haemoglobin was 16 g/100 ml; haematocrit 47%, white blood cell count 5,700/mm³ with a normal differential leucocyte count except for 5% eosinophils. The serum trypsin inhibitory capacity and chest X-ray were normal. Allergy skin testing revealed significant prick test reactions to tree and ragweed pollens.

Studies of lung function, which included spirometry, flow-volume loops, determination of airway resistance and thoracic gas volume in the pressure plethysmograph, were within normal limits. At each study period, plethysmography was performed first and the average of four reproducible measurements was used. Then, maximal expiratory flow-volume curves and spirometry were carried out in triplicate and the best effort used in computation. Because of the occupational history, inhalation challenge testing was carried out as described by Pepys (1973, 1975). Informed consent was first obtained from the patient. On two separate days, within 45 min of recording normal baseline values, inhalation exposures to fumes of phthalic anhydride were given for 75 sec. On the second exposure day, the patient was pre-treated with cromolyn sodium (sodium cromoglycate), 20 mg by Spinhaler®, 20 min before exposure to phthalic anhydride. Pulmonary function was studied at 15, 30, 60, 120, 300 and 360 min after the exposure. A planned exposure to a non-phthalic anhydride aerosol was not completed because of the patient's refusal to agree to further bronchial provocation studies.

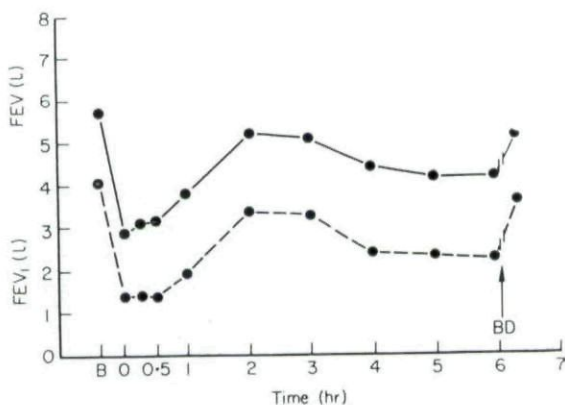


Fig. 1. The forced expired volume, FEV (●—●) and the forced expired volume in 1 sec, FEV₁ (●---●) plotted against time. The initial baseline value is B, and the value immediately following exposure to phthalic anhydride is at 0. Treatment with bronchodilators, BD, was given after 6 hr. Note the biphasic response with an immediate drop in volumes and a delayed drop at 3–4 hr.

Results

The patient exhibited immediate bronchoconstriction after a 75 sec exposure to phthalic anhydride fumes. Immediately after exposure, both the total forced expiratory volume (FEV) and the volume expired in 1 sec (FEV₁), fell to about 50% of the initial baseline value (Fig. 1). This effect was maximal within 1 hr and spontaneously returned toward normal by 120 min. Measurements of airway resistance (Raw) and thoracic gas volume (Vtg) confirmed the immediate deleterious effect (Fig. 2). There

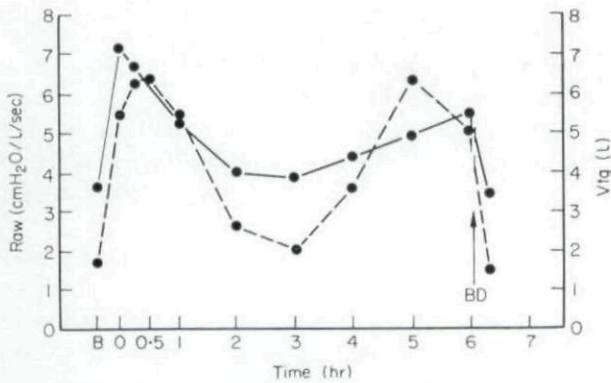


Fig. 2. The airway resistance, Raw (●---●) and the volume of thoracic gas, Vtg (●—●) following exposure at time 0 to phthalic anhydride. Note the immediate response and delayed response at about 4 hr, relieved by bronchodilators after 6 hr. There is both hyperinflation and bronchoconstriction as noted respectively in the Vtg and the Raw. B, Baseline; BD, treatment with bronchodilators.

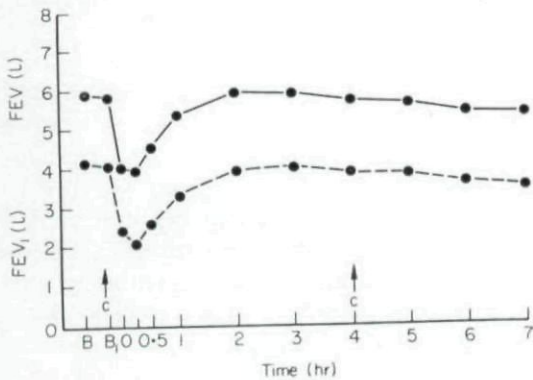


Fig. 3. The same variable as Fig. 1, with pretreatment with cromolyn before exposure to phthalic anhydride. Note the immediate bronchoconstrictor response persists with ablation of the delayed response at 3–4 hrs. ●—●, FEV; ●---●, FEV₁; B, baseline; B₁, baseline after cromolyn sodium; C, cromolyn sodium administration.

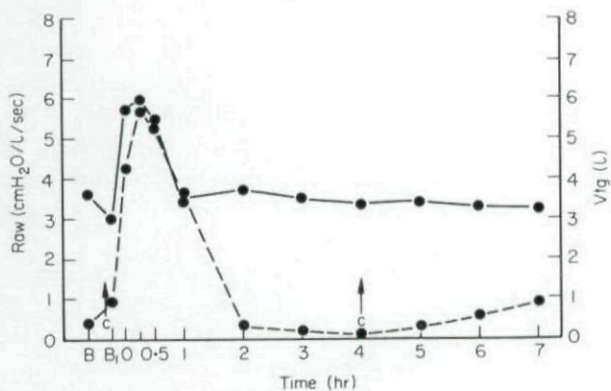


Fig. 4. The same variables as Fig. 2, with pretreatment with cromolyn sodium before exposure to phthalic anhydride. Note the persistence of the immediate bronchoconstrictor response with ablation of the delayed response at 4 hr. ●—●, Vtg; ●---●, Raw; B, baseline; B₁, baseline after cromolyn sodium; C, cromolyn sodium administration.

was an increase in Raw of over 300% of the initial value accompanied by hyperinflation as the volume of thoracic gas increased by more than 3 l, doubling the original lung volume. These values also returned toward normal by 2 hr.

Delayed bronchoconstriction was demonstrated by worsening of the measured variables by the fourth hour (Figs 1 and 2). There was prompt response of these abnormalities to the administration of an aerosol of isoproterenol bronchodilator after the measurements taken at 6 hr.

On the second exposure day, pretreatment with cromolyn sodium, 20 mg, was given just before the 75 sec exposure to fumes of phthalic anhydride (Figs 3 and 4). The cromolyn sodium treatment was repeated 240 min after exposure. Measurement of the same variables showed an inhibition of the late, but not the early bronchoconstrictor response to phthalic anhydride inhalation.

After this evaluation, the patient was advised to change to a job involving no phthalate exposure, or to use cromolyn sodium and bronchodilators in combination to handle the consequences of his occupational exposure. A serum RAST assay was negative.*

Discussion

The results indicate that asthma may occur in association with inhalation of phthalic anhydride fumes. The history strongly suggests prolonged occupational exposure as the sensitizing mechanism, although our data does not indicate the duration of exposure necessary to produce disease. While phthalic anhydrides have been regarded as irritating to the eyes and upper airways, we were able to find only one other report associating phthalic anhydride fumes with reversible airways obstruction (Maccia *et al.*, 1976). Taken together, these two reports clearly place phthalic anhydride in the group of organic chemicals causing occupational asthma including toluene diisocyanate (Pepys *et al.*, 1972a), aminoethyl ethanolamine (Pepys & Pickering, 1972), diphenyl-methane diisocyanate (Tanser, Bourke & Blandford, 1973) and other chemical agents (Seaton, 1975; Pepys, Pickering & Loudon, 1972b).

Mechanisms of production of occupational asthma are varied and frequently unknown. Immunological mechanisms have been inferred with a number of substances, but serious technological problems exist which interfere with the demonstration of immune responses to these materials by skin-testing, *in vitro* antibody assays or similar tests. Frequently, as in this case, we may infer an allergic mechanism from the fact that inhalation challenge exposure causes a dual, early and late bronchoconstrictor response as seen in asthma associated with organic dust inhalation (Pepys, 1969, 1975). Production of 'early' responses has been shown to correlate well with the presence of positive skin tests and specific IgE antibody in the serum. It is quite possible, however, that patients with hyperreactive airways may respond to low levels of an irritant inhalant with asthma on a non-immunological basis (Popa *et al.*, 1969).

IgE has been identified as the major immunoglobulin class producing tissue injury in most inhalant asthma where antigen-antibody reactions can be demonstrated. Asthmatic reactions to specific inhaled antigens can be 'early' (immediate), 'late' (several hours after exposure) or dual, combining both early and late reactions. Pretreatment with cromolyn sodium can inhibit both early and late reactions following specific antigen exposure (Kolotkin, Lee & Townley, 1974). Cromolyn sodium does not

*Kindly performed by Dr I. L. Bernstein and associates, University of Cincinnati School of Medicine.

protect against bronchoconstrictive effects of either histamine or methacholine aerosols (Ryo, Kang & Townley, 1971) although blocking of the bronchoconstrictive response to intravenous histamine has been reported (Ryo, Kang & Townley, 1976). Pepys (1969, 1973) postulated that cromolyn sodium pretreatment blocks the 'late' response by interference with the 'early', IgE mediated, type I response. Bryant and colleagues (Bryant, Burns & Lazarus, 1975) described the failure of cromolyn sodium pretreatment to block immediate bronchial reactions in patients in whom IgG antibody appears to act as the reagin.

While the patient reported by Maccia *et al.*, (1976) did have *in vitro* evidence of an anti-phthalate IgE antibody, our patient did not. Our negative RAST assay for IgE antibody does not exclude immunological asthma. An anti-phthalate IgE antibody may have either not been detectable or have been missed because of decay (the serum had been stored, frozen, for many months). It is also possible that a non-IgE mechanism was involved. The effect of cromolyn sodium in preventing the late asthmatic response to phthalic anhydride supports the hypothesis of an antigen-antibody reaction. Failure of cromolyn sodium to block the early response may be due to an IgG reagin or to the fact that the early response was a combined irritative and immunological event with the irritation not inhibited by cromolyn sodium.

This case not only confirms the role of phthalic anhydride as a cause of occupational asthma but raises the question of its potential as an inhalant trigger in other asthmatics. Phthalate exposure may occur by cutaneous (plastics), ingestant (food wraps), injectant (blood bags), and respiratory routes. Volatile exposures can occur most often in industry, but phthalates have been found in many areas, including the air inside automobiles (Graham, 1973). The potential for exposure of the asthmatic population is immense. Only time and detailed inquiry will indicate its relevance to chronic asthma.

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