

Recurrent nocturnal asthma due to tolylene di-isocyanate: a case report

A. SIRACUSA, F. CURRADI and G. ABBRITTI

Institute of Occupational Medicine, University of Perugia, Policlinico, Perugia, Italy

(Received 1 September 1977; accepted for publication 26 September 1977)

Summary

In a carpenter with a history of nocturnal dyspnoea, a bronchial provocation test with a tolylene di-isocyanate (TDI) activator elicited a non-immediate asthmatic reaction, followed by recurrent nocturnal asthma for five subsequent nights. Subsequently, the study of the circadian rhythm of airflow, registered during work, confirmed the presence of recurrent nocturnal asthma of occupational origin.

Introduction

It has been known for a long time that bronchial asthma often manifests itself most seriously during the night and early morning (Salter, 1882). Recently it has also been observed that asthmatic patients die more frequently during the night (Cochrane & Clark, 1975). In some cases asthma only manifests during the night: so-called recurrent nocturnal asthma.

Numerous attempts have been made to explain the causative mechanisms of nocturnal asthma. Reinberg, Ghata & Sidi (1963) have shown that nocturnal asthmatic attacks coincided with the lowest urinary excretion of 17-hydroxycorticosteroids, while Soutar *et al.* (1975) have demonstrated that cortisol infusion, given to avoid the nocturnal decline of steroids, did not prevent the fall in PEFR in five out of six patients with nocturnal and morning asthma. Clark & Hetzel (1977) have noticed that the nocturnal dip of PEFR is intimately related to sleep, not to posture. Turner-Warwick (1977) has considered several proposed aetiological factors of 'morning dipping' (allergic factors, posture, sleep patterns, hypoxaemia and carbon dioxide retention, endogenous cortisol levels and endogenous catecholamines). Turner-Warwick concludes that morning asthma is likely to be based on more than one mechanism.

In recent literature, some cases of recurrent nocturnal asthma of occupational origin have been reported. It has been demonstrated in workers exposed to Western red cedar (Gandevia & Milne, 1970), to formalin (Gandevia, 1970), to proteolytic enzymes (Mitchell, 1970; Mitchell & Gandevia, 1971), to ampicillin powder (Davies, Hendrick & Pepys, 1974) and to grain dust (Davies, Green & Schofield, 1976). Recurrent nocturnal asthma has also been documented in a printer after actual exposure to his work environment (Davies, R.J., personal communication, reported by

Correspondence: Dr F. Curradi, Istituto di Medicina del Lavoro, Policlinico, 06100 Perugia, Italy.

Pepys & Hutchcroft, 1975). It has also been suspected, but not documented, in workers exposed to osmium tetroxide and isocyanate (Gandevia, 1970). In some patients, it has been documented after a bronchial provocation test (Gandevia & Milne, 1970; Mitchell, 1970; Davies *et al.*, 1974, 1976).

We studied a carpenter with a clinical history of chiefly nocturnal attacks of bronchial asthma after exposure to two-stage varnishes. Bronchial provocation tests caused the onset of nocturnal asthma, which recurred for five consecutive nights, after a single 30 min exposure to a 'tolylene di-isocyanate (TDI) activator'. The diagnosis of recurrent nocturnal asthma and the aetiological role of the TDI contained in the varnishes were confirmed by subsequent study of the circadian rhythm of pulmonary function, during and after actual work. As far as we know, this is the first documentation of recurrent nocturnal asthma due to TDI.

Case report

A 40-year-old carpenter came to the hospital with a 3 year history of shortness of breath and cough. He had been a carpenter since the age of 14: until the age of 25, he worked in a small artisan shop; from the age of 25 to 28, in a saw-mill; from 28 to 37, in a parquet factory; and from the age of 37 onwards, in a furniture factory. He had no family history of asthma, hay fever or eczema, and had smoked about fifteen cigarettes a day since the age of 18. He had childhood eczema. After the age of 29, he developed contact dermatitis, with sensitivity to potassium dichromate and cobalt. He had no history of respiratory disturbances until 1973, although he was using plasticizer floor varnishes at work. In 1973, at the age of 36, after his first contact with a two-stage plasticizer floor varnish which had never been used before, he complained of shortness of breath and cough. The dyspnoea began 1-2 hr after exposure to the plasticizer, became progressively worse and reached its worst point during the night. He continued to manifest nocturnal dyspnoea for about a week, in spite of being away from work. Another brief exposure to the same varnish when he returned to work reproduced symptoms very similar to those mentioned above.

A short time later the patient changed jobs, and began to work in a furniture factory where he was occasionally exposed to varnishes used in the same work area, but not directly by him. In 1974, after occasional inhalation of a polyurethane varnish, he complained of recurrent nocturnal asthma for about a week, even though he did not go back to work when the symptoms began. On 6 July 1976, following a new exposure to a polyurethane varnish, he complained of dyspnoea that was worst during the night. In the following 2 weeks, he continued to have nocturnal shortness of breath, even though he left work immediately upon the onset of the symptoms.

He was admitted to hospital on 16 August 1976. He was symptom-free and there were no physical signs on examination. Initial investigation showed a total blood leucocyte count of $6100/\text{mm}^3$, and an absolute eosinophil count of $88/\text{mm}^3$. The chest roentgenogram, the arterial blood gases and the acid-base balance were normal. The respiratory function tests were all within the predicted range for his height (172 cm) and age.

Materials and methods

Skin tests

The skin prick method (Pepys, 1975) was used for skin testing and the results read at

30 min. The allergens used were the following: *Alternaria tenuis*, *Aspergillus fumigatus* and *A. terreus*, *Cladosporium herbarum*, *Merulius lacrymans*, *Sporobolomyces roseus*, yeasts, *Candida albicans*, mixed grass, shrub and tree pollens, extracts of cat, dog, hen and horse, house dust, *Dermatophagoides pteronyssinus*, milk, wheat, egg, fish and nuts. All of the extracts were prepared by Bencard Allergy Unit (Brentford, England).

Bronchial provocation tests

The patient was tested by exposure to polyurethane varnish and 2 days later to a TDI activator; varnish and activator were the two components of the two-stage polyurethane varnish used in the furniture factory where the patient worked. First, he applied the polyurethane varnish itself with a paintbrush to a wood surface in a small cubicle, and 2 days later this was followed by application in the same way of the TDI activator. Both the tests lasted for 30 min. FEV₁ was measured before each bronchial provocation test, then every 10 min for the first hr, every hr for 12 hr and then again at 24 hr. The FEV₁ was measured with a dry spirometer (Vitalograph). Body temperature was measured before each bronchial provocation test, then every hr for 12 hr, and then at 24 hr.

Determination of TDI vapour in air

During the bronchial provocation tests, a Dunlop-ICI TDI detector was operated in accordance with the manufacturer's instruction manual. This instrument is available from Universal Environmental Instruments (UEI, England). A Rustrak recorder, Model 288 (Rustrak Instruments, England) was connected to the instrument to give a continuous and permanent record of TDI concentrations. Determination of TDI in air was carried out during the 30 min of the bronchial provocation tests, and then during the 30 min immediately following the tests.

Circadian rhythm of pulmonary function

Measurements of the circadian rhythm of airflow in hospital, at home and during work were made with the 'Airflometer', Glaxo Laboratories Ltd, Greenford, Middlesex England (Friedman & Walker, 1975). By means of the Airflometer, the airflow is directly read on an indicator graduated in arbitrary AFM units (range 2–286 units), which correlated well with FEV₁ according to Friedman & Walker (1975). Measurements were made at 06.00, 10.00, 14.00, 18.00 and 22.00 hr, and also during the night, usually between 02.00 and 04.00, if the patient awoke spontaneously. During the measurement of the circadian rhythm of airflow at home and during work the patient was treated with sodium cromoglycate (20 mg q.i.d. in a Spinhaler) and salbutamol sulphate (0.2 mg aerosol b.i.d., at 06.00 and at 23.00).

Results

Respiratory function tests and arterial PO₂, PCO₂, and pH were all within normal limits (Tables 1 and 2). The prick tests with twenty-two common allergens were all negative. The chest X-ray was normal.

The bronchial provocation test with the polyurethane varnish (Fig. 1) provoked no reactions; there was no marked diurnal variation in pulmonary function and the body temperature did not rise above normal during the total observation period. The inhalation test with the TDI activator (Fig. 1) provoked a non-immediate asthmatic

Table 1. Pulmonary function tests on admission

Test	Actual	Predicted (%)
FEV ₁ (ml)	3931	102.1
VC (ml)	5117	100.5
FEV ₁ /VC (%)	76.8	—
MMFR (l/sec)	4.11	95.6
RV (ml)	1889	116.6
TLC (ml)	7006	104.4

Table 2. Arterial blood gases and pH on admission

Test	Result	Normal range
PO ₂ (mmHg)	86.7	80–110
PCO ₂ (mmHg)	45.7	34–46
pH	7.39	7.36–7.44

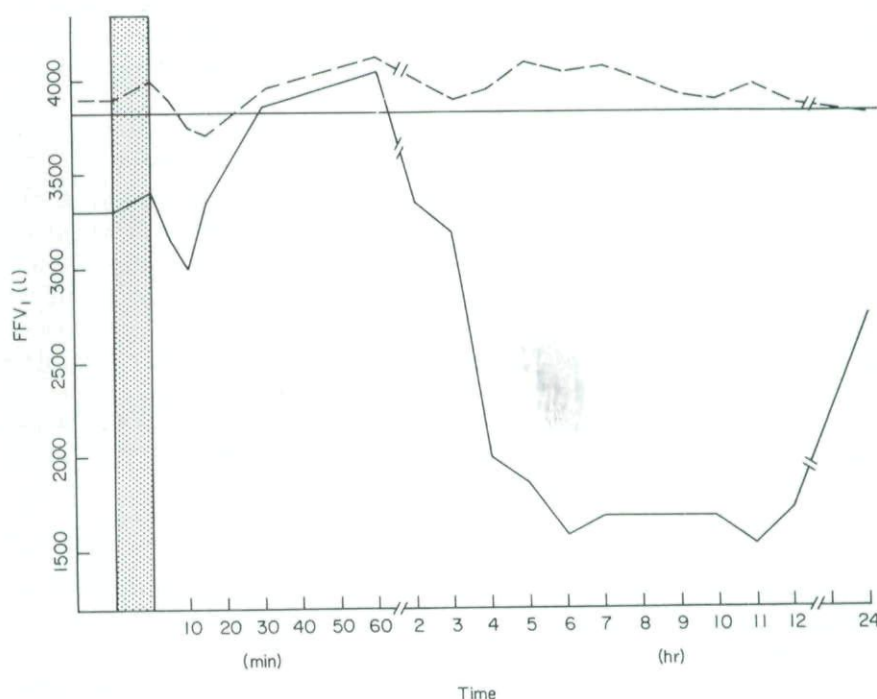


Fig. 1. No reaction to a 30 min challenge test with polyurethane varnish without activator (---). Non-immediate asthmatic reaction to 30 min challenge test with polyurethane activator (—). Stippled area shows the challenge. The horizontal line shows the predicted value.

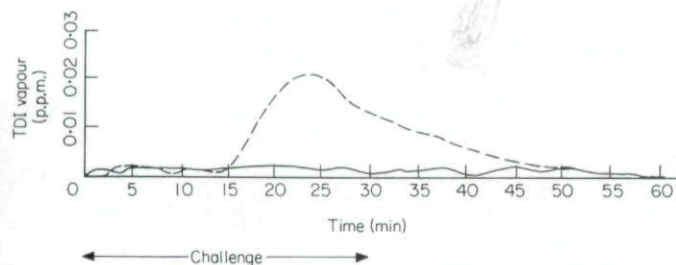


Fig. 2. Determination of TDI vapour in air. During challenge test with polyurethane varnish (—) practically no TDI was measured. During challenge test with activator (---) the content of TDI reached a maximum of 0.02 p.p.m.

reaction which came on after 4 hr, was maximal between 6 and 11 hr and was not completely resolved at 24 hr. During the non-immediate asthmatic reaction he developed shortness of breath. On physical examination at the height of the reaction, there were signs of airways obstruction with wheezing, widespread expiratory ronchi and marked prolongation of expiration. Body temperature rose slightly (37.6°C) at 12 hr after the test.

During the challenge with polyurethane varnish (Fig. 2), practically no TDI vapours were detected in the air, whereas during the challenge test with the activator the concentration of TDI in air reached a maximum of 0.02 p.p.m.

Measurement of the circadian change of airflow in hospital (Fig. 3) shows that the AFM units were maintained within normal limits until the second challenge test, made with the TDI activator. Afterwards, besides the non-immediate asthmatic reaction already described (Fig. 1), the patient began to show a recurrent nocturnal fall in airflow that only resolved 6 days after the test.

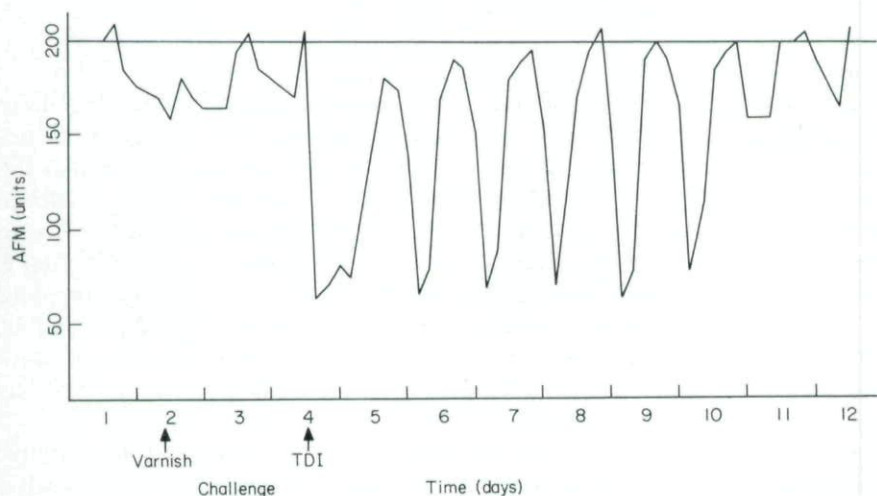


Fig. 3. Circadian rhythm of airflow after challenge tests with polyurethane varnish and TDI activator. Note that recurrent nocturnal asthma after the challenge test with TDI activator lasted for five nights. The horizontal line shows the predicted value.

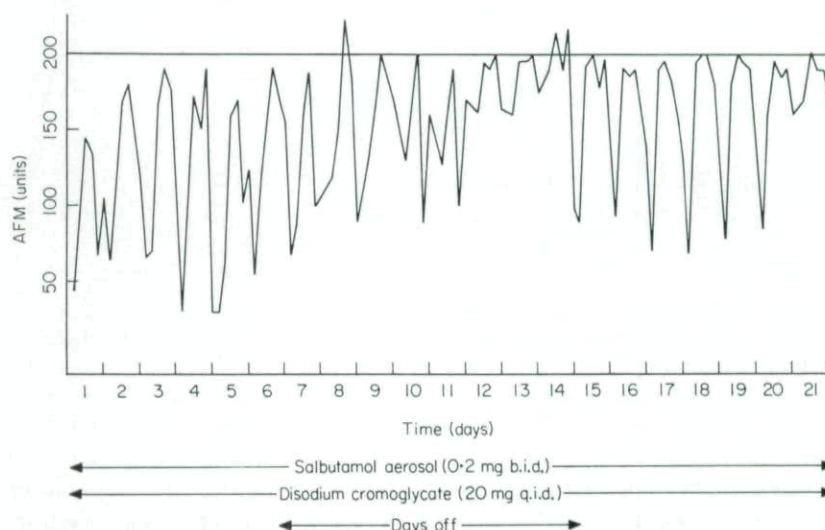


Fig. 4. Circadian change of airflow over the 3 successive weeks after returning to work. Note the airflow during days off (days 7–14) and the unresponsiveness to cromoglycate and salbutamol. The horizontal line shows the predicted value.

The patient, therefore, was discharged from hospital with the same instrument (Airflometer) that was used during his stay in hospital. 10 days after he was discharged, he began his regular work and occasionally came into contact with the polyurethane varnishes containing the TDI activator.

Fig. 4 shows the circadian change of airflow during the first 3 weeks after he returned to work. A recurrent nocturnal fall in pulmonary function is evident in the first and third week; in the second week, during which the patient was not at work, there was a tendency for improvement in pulmonary function, which became nearly normal after 5 days of absence from work.

Discussion

The clinical history of the patient pointed to recurrent nocturnal asthma. This diagnosis was confirmed by the observation period in hospital following the bronchial provocation test with the activator of the polyurethane varnish (Fig. 2), as well as the assessment by means of the Airflometer (AFM) during a work period. The challenge test with the TDI activator showed that the principal aetiological agent in the disease was TDI. Yet we found that a nocturnal fall of AFM units was registered after 8 days of abstention from work (day 14 of Fig. 4). Note that in the 3 days preceding this fall, practically normal pulmonary function was registered (days 12, 13 and 14 of Fig. 4). This permits the assumption that, even though TDI is the principal cause of his recurrent nocturnal asthma, other factors could have been involved, as previously suggested by Turner-Warwick (1977).

The mechanism by which TDI and the other substances capable of inducing recurrent nocturnal asthma (Western red cedar, proteolytic enzymes, ampicillin powder, grain dust, etc.) cause this disease is not clear.

The role of atopy in this case was doubtful since our patient had a positive personal history (childhood eczema and contact dermatitis), but the family history and the

prick tests were negative. Treatment with sodium cromoglycate (20 mg q.i.d. in Spinhaler) and with Salbutamol (0.2 mg aerosol b.i.d.) was ineffective for the prevention of the nocturnal asthmatic attacks, as already observed by Clark & Hetzel (1977). During the observation period, steroids were not given.

The challenge tests are a very valuable help in the diagnosis of occupational bronchial asthma and they often make possible the identification of the causative agents. Besides this, it seems to us that a prolonged study of the circadian rhythm of the pulmonary function should always be made, together with the other diagnostic investigations for bronchial asthma. This enables the identification of nocturnal asthma that otherwise could be difficult to establish, if clinical and functional tests are made only during the day. Finally, the study of the circadian rhythm of pulmonary function, carried out before and after a provocation test, makes it possible to determine whether or not the recurrent nocturnal asthma is caused by the challenge test or pre-exists by itself.

Acknowledgments

We wish to thank Miss N. Baker and Mr A. Binucci for their excellent technical assistance.

References

- CLARK, T.J.H. & HETZEL, M.R. (1977) Diurnal variation of asthma. *British Journal of Diseases of the Chest*, **71**, 87.
- COCHRANE, G.M. & CLARK, T.J.H. (1975) A survey of asthma mortality in patients between ages 35 and 64 in the Greater London hospitals in 1971. *Thorax*, **30**, 300.
- DAVIES, R.J., GREEN, M. & SCHOFIELD, N.McC. (1976) Recurrent nocturnal asthma after exposure to grain dust. *American Review of Respiratory Disease*, **114**, 1011.
- DAVIES, R.J., HENDRICK, D.J. & PEPYS, J. (1974) Asthma due to inhaled chemical agents: ampicillin, benzyl penicillin, 6-amino penicillanic acid and related substances. *Clinical Allergy*, **4**, 227.
- FRIEDMAN, M. & WALKER, S. (1975) Assessment of lung function using an air-flow meter. *Lancet*, **i**, 310.
- GANDEVIA, B. (1970) Occupational asthma, part I. *The Medical Journal of Australia*, **2**, 332.
- GANDEVIA, B. & MILNE, J. (1970) Occupational asthma and rhinitis due to Western red cedar (*Thuja plicata*), with special reference to bronchial reactivity. *British Journal of Industrial Medicine*, **27**, 235.
- MITCHELL, C.A. (1970) Occupational asthma due to Western or Canadian red cedar (*Thuja plicata*). *The Medical Journal of Australia*, **2**, 233.
- MITCHELL, C.A. & GANDEVIA, B. (1971) Respiratory symptoms and skin reactivity in workers exposed to proteolytic enzymes in the detergent industry. *American Review of Respiratory Disease*, **104**, 1.
- PEPYS, J. (1975) Skin testing. *British Journal of Hospital Medicine*, **14**, 412.
- PEPYS, J. & HUTCHCROFT, B.J. (1975) Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *American Review of Respiratory Disease*, **112**, 829.
- REINBERG, A., GHATA, J. & SIDI, E. (1963) Nocturnal asthma attacks: their relationship to the circadian adrenal cycle. *Journal of Allergy*, **34**, 323.
- SALTER, H.H. (1882) *Asthma: its Pathology and Treatment*, 1st American edn, p. 33. William Wood, New York.
- SOUTAR, C.A., COSTELLO, J., IJADUOLA, O. & TURNER-WARWICK, M. (1975) Nocturnal and morning asthma: its relationship to plasma corticosteroids and response to cortisol infusion. *Thorax*, **30**, 436.
- TURNER-WARWICK, M. (1977) On observing patterns of airflow obstruction in chronic asthma. *British Journal of Diseases of the Chest*, **71**, 73.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.