

Tetracycline asthma—a case report*

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Summary

A mechanic working in the antibiotic capsuling section of a pharmaceutical company developed asthmatic attacks 1 year after starting work. His occupation involved exposure to a variety of chemical agents including tetracycline. He developed immediate wheal and flare reaction to the intradermal test and an immediate (type 1) asthmatic response to intradermal, inhalation and oral challenge tests with tetracycline. On leaving the tetracycline plant he became symptom free.

Introduction

Bronchopulmonary reactions to allergen inhalation tests may be early (immediate) or late in the time of onset and bronchial (asthmatic) or alveolar in location (Hargreave & Pepys, 1972; Booij-Noord, Orie & de Vries, 1971). Early responses begin within 10 min, reach maximum after 20–30 min and remit completely after 1–3 hr. Late responses usually begin 4–6 hr after tests and reach a maximum at about 8–12 hr. These reactions may resolve within 24 hr or sometimes persist for several days.

Allergic reactions to tetracycline are well documented (Peter & McKenzine, 1954; Finland, 1951; Gardner, 1953). The commonest manifestations were gastrointestinal; urticaria, angioedema and skin rashes were also reported. Few cases of generalized anaphylactic reactions after the administration of tetracycline were noted. Asthma occurring alone as a manifestation of allergy to tetracycline has not been reported,† though it may occur as part of generalized anaphylaxis (Bedford, 1951; Feltner & Baer, 1965).

Although exposure to tetracycline occurred in this patient by contact and inhalation of fine dusts, it was important to examine the effect of oral administration of the drug as well.

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† Following the preparation of this report, the authors have noted the case report of 'Allergy to a tetracycline preparation' by I. W. Fawcett and J. Pepys (*Clinical Allergy*, 6, 301–306, 1976).

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Materials and methods

Skin tests

Intradermal tests were done with a battery of sixty inhalant allergens. Intradermal tests, 0.02 ml, with solutions of tetracycline (chemically pure as well as commercial), chloromycetin, streptomycin and nystatin (0.5 mg/ml) were done. Prick and intradermal tests were done with solution of sodium penicillin (0.5 u/ml). Control tests were performed with comparable amounts of buffered saline. FVC and FEV₁ were recorded before and after the tests as described below under 'inhalation challenge'.

Body temperature, eosinophil and white blood cell counts

Mouth temperature was recorded before, 30 min, 1, 4, 8, 12, 24 and 48 hr after each provocation test. Peripheral blood leucocyte counts were done before 4, 8 and 24 hr after the tests.

Inhalation challenge tests

Powdered allergen and placebo were nebulized through a Spinhaler (Fisons Ltd). 'Analar' lactose, 100 mg, was used as control; bronchial provocation tests were made with commercial tetracycline 100 mg (tetracycline hydrochloride), chemically pure tetracycline 100 mg (supplied by Indian Drugs and Pharmaceuticals Limited, Rishikesh), chloromycetin, streptomycin, nystatin and penicillin (100 mg each). FVC and FEV₁ were measured before challenge, 2, 5 and every 10 min for 1 hr after the challenge, hourly for 8 hr, and at 12, 24 and 48 hr. The provocation challenge was terminated when the patient developed chest symptoms.

Oral challenge tests

One capsule of tetracycline hydrochloride (250 mg) was given orally. This was the same commercial sample as was used for inhalation tests. FVC and FEV₁ were recorded as described above.

Case history

A Sikh male, aged 28 years, employed for the past 2 years as a mechanic in the capsule section of Indian Drugs and Pharmaceuticals Ltd (IDPL) was first investigated in March 1975 for asthma which developed 1 year after starting work in the factory. He was certain that it was due to exposure to antibiotic dusts. He developed cough and wheeze with breathlessness whenever he entered his section of the factory, the symptoms lasting for 3-4 hr. His symptoms gradually increased in duration and severity and he was away from work for many days a month. He noticed that he improved on keeping away from the tetracycline plant.

He had no previous history of asthma, rhinitis, eczema, urticaria or drug allergy. He is a non-smoker and has a child who has no asthma or allergic disorder. His maternal grandmother had asthma.

No abnormality was detected on clinical examination. His chest X-ray, haemoglobin, total and differential leucocyte counts and stool were normal. Intradermal tests with sixty allergens (pollen, fungi, dusts danders, insects, feathers and house dust mite, *D. farinae*) were negative.

Intradermal test with pure tetracycline gave rise to a 4+ reaction (Shivpuri & Aggarwal, 1969), and he developed wheeze and dyspnoea within 10 min which

Table 1. Pulmonary function tests on admission

	Observed	Percentage predicted
FEV ₁ (ml)	3568	100
FVC (ml)	4148	110
FEV ₁ % VC	86	
VC (ml)	4148	110
FRC (ml)	3500	100
TLC (ml)	6900	
RV/TLC	33.4	

Table 2. Results of provocation tests

Materials	Amount used (mg)	No. of inhalations	Date of challenge	Maximum % fall from basal FEV ₁	Time at which max. fall occurred (after challenge) (min)
Inhalation test					
Lactose	100	4	16.3.75	1.9	10
Tetracycline	100	2	29.3.75	54.7	20
(commercial)					
Tetracycline	100	2	17.3.75	46.4	20
(purified)					
Chloromycetin	100	4	1.4.75	5.1	2
Nystatin	100	4	31.3.75	4.2	10
Streptomycin	100	4	2.4.75	1.7	60
Penicillin	100	4	4.4.75	1.8	30
Intradermal test					
Tetracycline	0.5 mg/ml (0.02 ml)	—	14.3.75	30.7	10
Oral challenge					
Tetracycline	250	—	20.3.75	46.4	50

was relieved by the injection of 0.5 ml. adrenaline subcutaneously. There was no delayed response. Intradermal tests with the same dose of chloromycetin, Nystatin, streptomycin and penicillin were negative. His pulmonary function tests on admission are shown in Table 1.

Readings of FVC and FEV₁ before and at different intervals after intradermal tests as well as inhalation provocation tests are shown in Table 2.

He was transferred from the production section to the administrative block in May, 1975 and has had no further asthma.

Results

Control

Inhalation of placebo did not show any significant reduction in FEV₁ (Fig. 1). The basal FEV₁ was constant on all occasions when it was recorded.

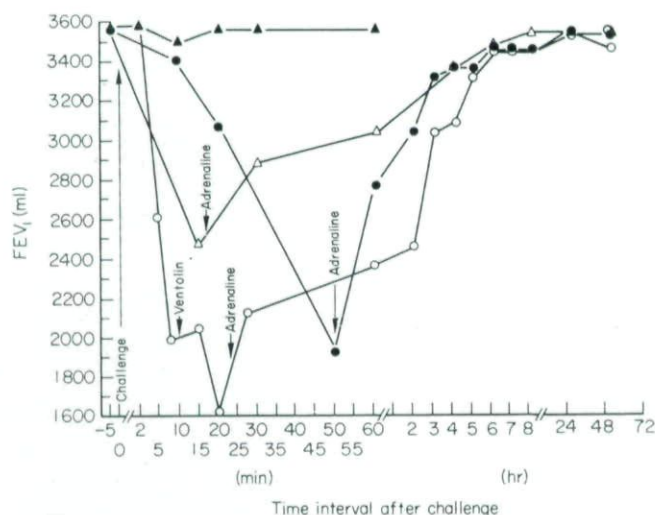


Fig. 1. Bronchial response to tetracycline. $\blacktriangle$ — $\blacktriangle$, After buffer saline 0.5 ml; $\triangle$ — $\triangle$, after skin test 0.5 mg/ml; $\circ$ — $\circ$, after inhalation 100 mg; $\bullet$ — $\bullet$, after ingestion 250 mg.

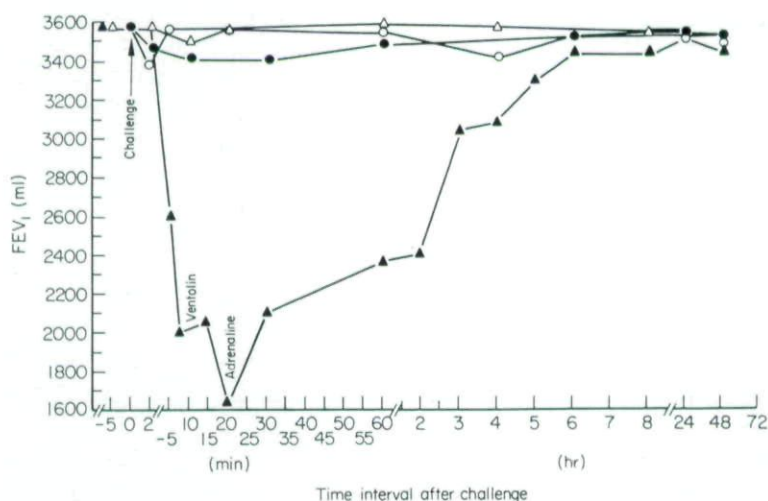


Fig. 2. Bronchial response to inhalation challenges with various antibiotics. $\triangle$ — $\triangle$, Lactose 100 mg; $\blacktriangle$ — $\blacktriangle$, tetracycline 100 mg; $\circ$ — $\circ$, chloromycetin 100 mg; $\bullet$ — $\bullet$, nystatin 100 mg.

Allergen inhalation tests

The patient was free of symptoms and signs when he was subjected to inhalation challenge with an interval of more than 2 days between tests. The results (Table 2) are expressed as the maximum percentage fall from the basal FEV_1 . A response was considered asthmatic when FEV_1 fell by more than 20% of the prechallenge level (Figs 1 and 2).

The induced asthmatic response to tetracycline was immediate (type I) developing within 20 min of inhalation challenge and intradermal test, and within 50 min of oral

challenge (Fig. 1). The patient developed urticaria after the oral challenge test which resolved on injection of adrenalin and administration of Avil. The FEV₁ returned to near normal by 6 hr and there was no late asthmatic response (Fig. 2).

The oral temperature did not rise above normal during the provocation tests or for 2 days after it. There was no leucocytosis or eosinophil cell response to the inhalation challenge.

Discussion

Tetracycline, commercial as well as pure, gave strong immediate responses on provocation tests, skin tests and oral challenge as well as inhalation, in this patient. Immediate and late asthmatic responses are known to occur on inhalation challenge with pollen (Robertson *et al.*, 1974), house dust (Booij-Noord *et al.*, 1971), house dust mite (McAllen, Assem & Maunsell, 1970), fungi (McCarthy & Pepys, 1971) and antibiotics (Davies, Hendrik & Pepys, 1974). Anaphylactic reactions to tetracycline have been reported (Bedford, 1951; Feltner & Baer, 1965). It is interesting to note that asthma occurring as a sole manifestation of tetracycline allergy has not been reported in more than 30 years of its use. The patient himself suspected the cause of his asthma and came to us well aware of it. The patient showed no evidence of airway obstruction on initial examination and there was no significant variation of FEV₁ on control days. Such stable control measurements allow confident assessment in this type of study.

There was no late asthmatic (type III) response in this case of the sort described with other antibiotics, chemicals and organic dusts (Davies, Hendrick & Pepys, 1974; Mitchell & Gandevia, 1971; Pickering, Batten & Pepys, 1972; Gandevia & Milne, 1970).

Asthmatic responses are elicited frequently after intradermal skin tests, as was the case here, and it is worth making respiratory function tests before and for some time after skin tests. In this patient immediate asthmatic responses were produced by two different commercial makes of tetracycline and by its chemically pure form, and also by oral challenge. This rules out the possibility of impurities present in the commercial sample being the cause of such responses.

When the patient kept away from the production section in another area where there was no chance of exposure to tetracycline dust, he became symptom free.

Acknowledgment

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