

Bronchial asthma due to spiramycin and adipic acid

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Summary

Two cases of bronchial asthma due to spiramycin in workers of a pharmaceutical factory are reported. The subjects complained of cough, breathlessness and symptoms of asthma at work when coming into contact with spiramycin's powder. The symptoms cleared when away from work for more than 3 or 4 days.

Inhalation challenge tests by aerosolization of solutions of spiramycin reproduced asthmatic reactions dual in type in both patients, the immediate component of the response has not been previously described for this antibiotic.

Furthermore, one of the patients developed an immediate asthmatic reaction also after inhalation of a solution of adipic acid, and additive to bind spiramycin and diminish its irritant action. The reaction was obtained at a non-irritant concentration of the acid, was reproducible and inhibited by previous administration of sodium cromoglycate: this finding and the failure to elicit the reaction in the other patient suggest a hypersensitivity reaction to this substance.

Introduction

Asthmatic syndromes due to chemical compounds are increasing in frequency. Particularly, many cases of asthma due to antibiotics are reported among pharmaceutical industry workers; e.g. one case of asthma due to spiramycin has been described in a worker by Davies and Pepys (1975), showing a dose-dependent delayed reaction to the bronchial challenge test.

Further, Paggiaro, Loi and Toma (1979) reported the case of a non-atopic woman who worked as a chick breeder handling poultry feed containing spiramycin and who complained of asthma and dermatitis. In this case, the bronchial challenge test with the chick feed containing the antibiotic reproduced symptoms with a late asthmatic response and leucocytosis.

In this paper, we report on two workers in a pharmaceutical factory who developed asthma on coming into contact with the powder of spiramycin adipate.

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The bronchial challenge test with spiramycin provoked a dual asthmatic reaction in both patients.

Since spiramycin was in the form of a salt of adipic acid (a bicarboxylic acid used as a general additive and in this case to diminish the irritant power of spiramycin) we tested the patients also with adipic acid alone: in one out of the two subjects the inhalation of a non-irritant concentration of adipic acid elicited an immediate asthmatic reaction, which was inhibited by the previous administration of sodium cromoglycate.

Materials and methods

Skin tests

Intradermal skin tests were made with a battery of common inhalants; patch tests were performed with a series of substances used in the pharmaceutical factory: solutions of adipic acid, spiramycin, vitamins and paraphenyldiamine.

Inhalation challenge tests

Bronchial challenge tests were carried out submitting the patients to inhalations, by a compressed-air aerosolizer, of 2 ml of the following solutions:

- 1 saline solution as a control;
- 2 spiramycin adipate: 0.1, 1, 10 mg/ml in saline solution;
- 3 adipic acid: 0.1, 1, 10 mg/ml in saline solution; and
- 4 spiramycin base: 0.1, 1, 10 mg/ml in saline solution.

Each substance was tested on a different day.

Respiratory functions were monitored by using a bell spirometer Volumograph® to measure FEV₁, VC, FEF₂₅₋₇₅ and a Siregnost® FD5 Siemens to measure airways' resistances (Ros) with the forced oscillatory method. These measurements were taken before the challenge, immediately after each inhalation, and after 15, 30, 60 min and hourly for the subsequent 9 hr, then 24 hr after the last inhalation.

Each test was interrupted when clinical features suggested a definite asthmatic reaction and a fall of 15% of the FEV₁ or 35% of FEF or a rise of 70% of Ros were measured. On the days preceeding the specific bronchial challenge each patient was submitted to a specific provocation test with acetylcholine delivered by a compressed-air aerosolizer in three different doses (500, 1000, 1500, µg).

Case history

Case No. 1

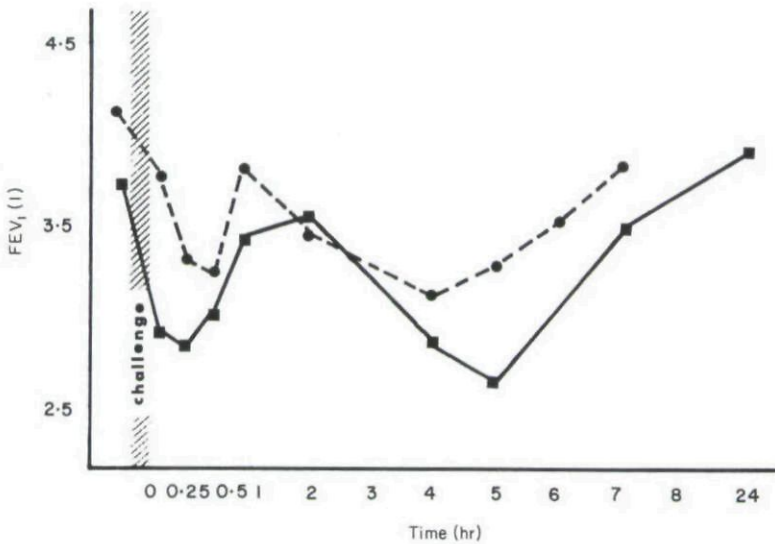
S.C., male, aged 42, has been employed in a pharmaceutical factory for 17 years as a warehouse man; during the last 3 years he began to complain of breathlessness when occasionally coming into contact with spiramycin's powder. He was admitted to hospital on 25 May 1981 for bronchial asthma.

He had no previous or family history of asthma, hay fever or eczema; no previous record of drug allergy and had never smoked cigarettes.

There was no abnormality on physical examination. His respiratory function tests on admission are shown in Table 1. Total serum IgE by PRIST (IgE test, Pharmacia) was 11.2 iu/ml. Radial immunodiffusion for immunoglobulins IgG, IgA and IgM gave normal values.

Table 1. Respiratory function tests for case No. 1 on admission

	Actual	% Predicted
FEV ₁	4.0 litres	102
VC	5.1 litres	100
FEV ₁ /VC	78%	
CO gas transfer factor (single breath)	36 ml/min/mmHg	120

**Fig. 1.** Patient S.C.: inhalation challenge test with spiramycin adipate (solid line) and effect of sodium cromoglycate on the test (broken line).

Intradermal tests showed a slight response to housedusts; RAST to the same was negative. Patch tests were negative. Acetylcholine test was positive at a dose of 1500 μ g. An asthmatic reaction dual in type (Fig. 1) followed bronchial challenge with spiramycin adipate at a concentration of 1 mg/ml: FEV₁ falling by 25% and FEF by 51% 15 min after the challenge, and by 30 and 77% respectively after 4 hr.

During the night the patient developed sneezing, rhinorrhea and bouts of cough.

On a different day, 40 mg of sodium cromoglycate inhaled 30 min before the challenge with spiramycin adipate and after 3 hr did not prevent the reaction though it modified its pattern giving a slighter response (Fig. 1). BPT performed with adipic acid alone did not induce any reaction.

Case No. 2

G.P., male, aged 47, began his job in the factory in 1974. He was employed as a store man for 1 year, and thereafter in the production of food. Since 1979 his job has consisted in pouring spiramycin and other antibiotics from containers into an open

Table 2. Respiratory function tests for case No. 2 on admission

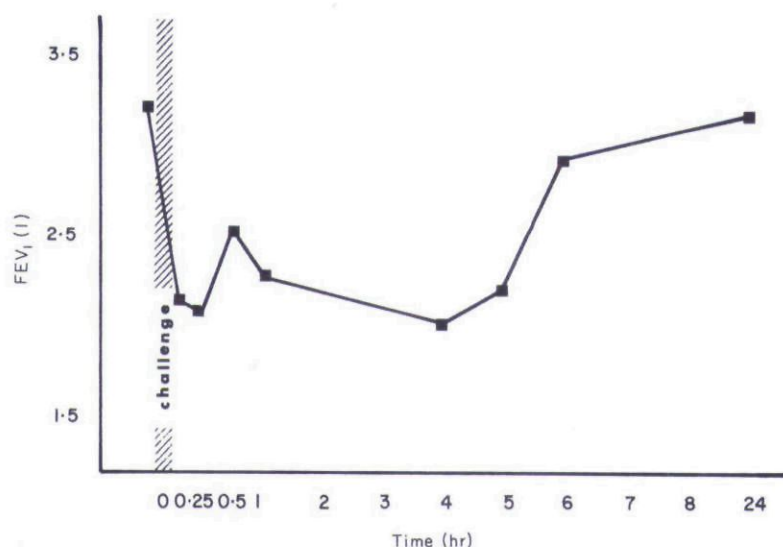
	Actual	% Predicted
FEV ₁	2.7 litres	80
VC	3.8 litres	100
FEV ₁ /VC	71%	
CO gas transfer factor (single breath)	31 ml/min/mmHg	100

cistern containing water at 35°C. In summer 1980 (after 6–7 months of work with spiramycin) he developed cough, frothy sputum and shortness of breath at work; he complained also of anosmia. The symptoms were so serious that the patient left his work many times for long periods. He was admitted to our hospital on 8 July 1981.

He had no previous or family history of allergic diseases. There was no abnormality on physical examination. Total IgE by PRIST were 600 iu/ml (N=122 iu/ml); the other Ig subclasses by radial immunodiffusion were normal. His respiratory function tests on admission are shown in Table 2.

Intradermal tests showed a slight reaction to housedusts and some vegetable extracts, but RAST to the same was negative. Patch tests gave a reaction to paraphenylenediamine.

Acetylcholine test was positive at a dose of 1000 µg. BPTs were made, first, with spiramycin adipate, (Fig. 2) eliciting an immediate and prolonged asthmatic reaction at a concentration of 10 mg/ml, and with adipic acid, (Fig. 3) which provoked at the same concentration, an immediate reaction that was inhibited by previous administration of 40 mg of sodium cromoglycate. After recovery the patient was discharged and ceased working in the spiramycin-producing factory.

**Fig. 2.** Patient G.P.: inhalation challenge test with spiramycin adipate.

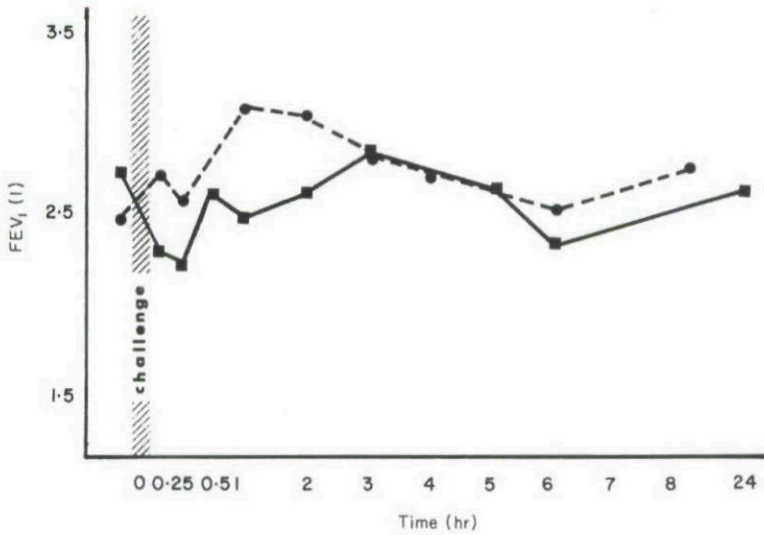


Fig. 3. Patient G.P.: inhalation challenge test with adipic acid (solid line) and effect of sodium cromoglycate on the test (broken line).

On a second admission to the hospital (in February 1982) BPTs were performed with saline solutions of spiramycin in base form and repeated with solutions of adipic acid, in order to assess the reproducibility of this test.

BPT with spiramycin base gave an asthmatic reaction dual in type (Fig. 4) at a concentration of 0.1 mg/ml: FEV₁ falling by 20% and FEF by 56% after 15 min and by 45 and 50% respectively within the 6th hr.

The patient suffered cough and dyspnoea: on physical examination there were

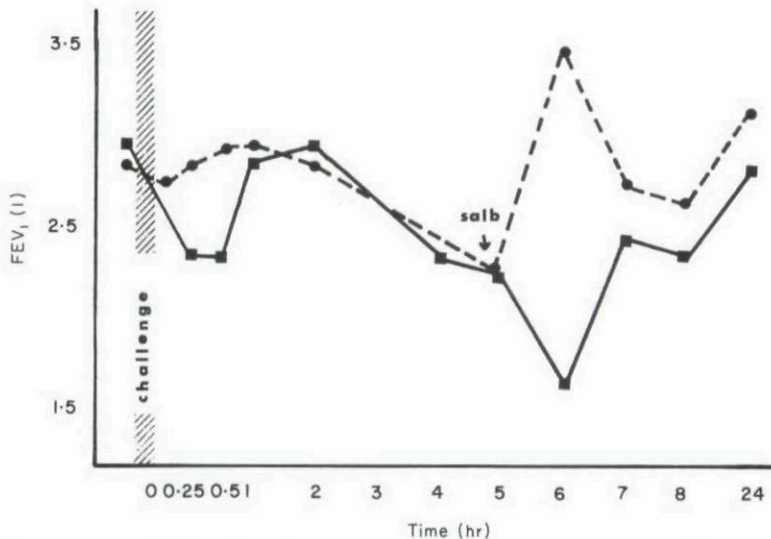


Fig. 4. Patient G.P.: inhalation challenge test with spiramycin base (solid line) and effect of sodium cromoglycate on the test (broken line; at 5th hr salbutamol was given).

some whistling rhonchi. At the 8th hr respiratory functions were unchanged; salbutamol was given.

On a different day BPT was repeated: 40 mg of sodium cromoglycate were given 30 min before the challenge and after 3 hr. The immediate reaction was prevented but during the 4th hr the patient experienced an asthmatic reaction with chest tightness and cough, FEV₁ falling by 21%; salbutamol was given. BPT with adipic acid reproduced an immediate asthmatic reaction at the same concentration as the previous test (10 mg/ml) FEV₁ falling by 20% and FEF by 47% after 15 min. This reaction was inhibited by the previous administration of sodium cromoglycate.

Discussion

Asthma due to spiramycin has been reported and confirmed by bronchial challenge tests (Davies & Pepys, 1975; Paggiaro *et al.*, 1979). An Italian long-term study (Nava, 1976) in a spiramycin-manufacturing factory showed the increasing skin positivity to patch or prick tests with the antibiotic in forty-one of 305 workers (13%) over a time varying from 2 months to 6 years from exposure; thirty-seven of these forty-one workers were also symptomatic (asthma, rhinitis and urticaria).

The mechanism by which spiramycin acts as an allergen is not known.

In our cases, the inhalation of the antibiotic in adipate form provoked in both patients an asthmatic response starting a few minutes after the challenge: in case No. 1 the reaction was dual in type, while in case No. 2 a unique, intense and prolonged bronchoconstriction was observed. The latter patient was also sensitive to adipic acid alone, and the repetition of the test with spiramycin in base form elicited a dual asthmatic reaction. We suggest that probably the unique, prolonged bronchoconstriction obtained in the first test was an effect of summation between the actions of spiramycin and adipic acid on the immediate component of the response, thus producing a different reaction pattern.

However, in both cases we observed an immediate component of the response which had not previously been obtained either by Davies and Pepys (1975) or by Paggiaro *et al.* (1979). This immediate component was prevented by the previous administration of sodium cromoglycate in case No. 2, but was not effective in case No. 1.

Furthermore as shown, one of our patients developed an immediate asthmatic reaction after inhalation of adipic acid. We are not aware of other reports of bronchial asthma due to this substance. Adipic acid is a dicarboxylic acid used in various manufactures (plastic & food stuffs) and as a general additive, for its buffer and neutralizing power (Candura, 1974; Sax, 1975).

Malten and Zielhuis (1965) reported a delayed cutaneous hypersensitivity to a patch test with adipic acid in a laboratory worker in a chemical factory producing polyester resins. In our subject, patch testing was negative.

The immediate asthmatic reaction elicited by inhalation of 2 ml of a 1% solution of adipic acid was prevented by the previous administration of sodium cromoglycate. This fact, the low concentration of the provocation dose, the failure to elicit the reaction in patient No. 1, and the reproducibility of the test after several months suggests a hypersensitivity to adipic acid mediated by a type I mechanism.

Our finding of an asthmatic reaction to a substance originally bound to a molecule (spiramycin) with the specific goal of diminishing its irritant power, focuses on the problem of symptoms due to additives, in a manufacturing process.

We support the view that in allergologic surveys, it is important to consider the possible role of the so-called 'inert' substances, such as additives, preservatives and colorants.

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