

Respiratory disease due to sulphasalazine

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Summary

A patient is described who developed a pulmonary hypersensitivity reaction to sulphasalazine used in the treatment of his ulcerative colitis. Challenge testing demonstrated that the patient was sensitive to the sulphapyridine component of the drug. The pulmonary response consisted of an immediate bronchial obstructive reaction and a late parenchymal reaction with fall in gas transfer factor. Detailed immunological testing failed to define the mechanisms of drug toxicity.

Introduction

Sulphasalazine is a drug widely used in the management of ulcerative colitis. It is a compound of a sulphonamide and a salicylate, two classes of drugs with known pulmonary toxic effects. This paper reports a study of the respiratory and immunological effects of sulphasalazine administered to a patient who had developed a pulmonary hypersensitivity to the drug, in an attempt to define its mode of action.

Material and methods

(1) *Pulmonary function*

Ventilatory capacity was measured by a dry spirometer, lung volumes by the closed-circuit helium dilution technique (Bates & Christie, 1950) and transfer factor for carbon monoxide by the single breath technique (Ogilvie *et al.*, 1957). Blood obtained by brachial artery cannulation was analysed by the Astrup micro-method.

(2) *Immunological studies*

(a) *Haemagglutinating antibody.* Sulphasalazine at 1 mg/ml in 0.01 M phosphate buffered saline pH 7.2 (PBS) was centrifuged at 10,000 *g* for 10 min and the supernatant coupled to the patient's red cells and rabbit red cells (Chusid & Atkins, 1972) and to formalized tanned sheep red cells (Mellors *et al.*, 1959). Haemagglutinating titres

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were determined using serial two-fold dilutions of patient's and control sera in PBS and sulphasalazine-coated red cells.

(b) *Sulphasalazine-binding immunoglobulin.* Sulphasalazine (0.5 ml at 3, 10 and 30 $\mu\text{g/ml}$ in PBS) was incubated with 0.5 ml aliquots of patient's and control sera for 2 hr at 37°C followed by 16 hr at 4°C. Immunoglobulins were precipitated by (1) rabbit anti-human immunoglobulin, 0.5 ml, and (2) saturated ammonium sulphate, 1.0 ml. Precipitates were washed twice in cold saline or half saturated ammonium sulphate respectively and dissolved in 0.1 M sodium hydroxide (3.0 ml). Absorption values were determined at 460 m μ using the SP800 twin beam spectrophotometer. (The extinction of sulphasalazine at 1% in 0.1 M sodium hydroxide at 1 cm path length was determined to be 750.)

(c) *Complement utilization.* Sequential blood samples taken before and after the challenge with sulphasalazine were assayed for complement using sheep red cells sensitized with rabbit anti-sheep red cell, determining haemoglobin release at 415 m μ .

(d) *Sulphapyridine-binding immunoglobulin.* The binding capacity for the sulphapyridine component of sulphasalazine was determined after the second challenge test. The techniques were the same for sulphasalazine binding except that the precipitate, dissolved in sodium hydroxide, was re-precipitated with 2.5 ml of 5% trichloroacetic acid, centrifuged at 10,000 g for 10 min and absorption at 308 m μ used to detect sulphapyridine in the supernatant.

(e) *Leucocyte migration inhibition.* Tests of inhibition of leucocyte migration were performed by the technique of Federlin *et al.* (1971) using sulphasalazine at 5.50 and 500 $\mu\text{g/ml}$. Migration indices in tissue culture medium 199 containing 10% foetal calf serum were calculated by comparison. Healthy control leucocytes were also tested with the same concentrations of sulphasalazine.

Case history

A non-smoking 46-year-old man presented in November 1971 with a history of bloody diarrhoea, abdominal pain and weight loss of 6 months duration. He had no history of previous respiratory symptoms, nor was there any personal or family history of allergy. Abnormalities on examination were confined to the abdomen and rectum and the diagnosis of ulcerative colitis was confirmed by barium enema, sigmoidoscopy, and rectal mucosal biopsy.

Investigations showed a haemoglobin of 11.8 g%, the red cells being hypochromic. There was a normal white cell count and eosinophil count and a blood sedimentation rate of 19 mm/hr Westergren. Total protein was 7.0 g% with a slight increase in the gamma globulin. The alkaline phosphatase was 113 i.u./l. Liver biopsy showed pericholangitis with mild portal tract lymphocytic infiltration without cholestasis.

Treatment with sulphasalazine 1 g four times daily and ferrous sulphate 200 mg three times daily was started on 11 November 1971. This was supplemented by prednisone enemata in December 1971 and oral prednisone 15 mg daily in February 1972. He slowly improved and when the liver function tests had returned to normal the oral prednisone was reduced gradually, being stopped at the end of March 1972. He continued taking sulphasalazine 1 g four times daily. Three months after stopping prednisone he complained of mild exertional dyspnoea, together with an unproductive cough. He had felt unwell and feverish since stopping the steroids in spite of good control of his intestinal symptoms.

Examination showed repetitive end inspiratory crackles at both lung bases but no

other abnormality. The chest radiograph showed a patchy alveolar filling pattern with ill defined nodular shadows throughout both lung fields. The haemoglobin was 15 g% with a normal blood film and white cell count. The blood sedimentation rate was 15 mm/hr. Serum proteins were normal and anti-nuclear factor was not detected. The electrocardiogram was normal. The sputum contained none of the stigmata of allergic bronchitis and no pathogens were isolated.

At the end of July 1972 sulphasalazine was suspected to be the cause of his symptoms and was stopped. His respiratory symptoms gradually improved and he was symptom-free when seen on 10 August 1972. Nevertheless, basal lung crackles were still present when he was admitted for further investigation in September 1972, though the chest radiograph revealed no abnormality at this time. Following investigation he has been given a card warning of the dangers of sulphonamides and has remained free of respiratory symptoms.

Table 1. Lung function tests while taking sulphasalazine (3 August 1972) and 6 weeks after stopping the drug

Date	Vital capacity (litres)	Forced expiratory volume (1 sec) (litres)	$\frac{FFV_1}{FVC}$ %	Residual volume (litres)	Total lung capacity (litres)	Transfer factor (ml/min/mm Hg)
3 August 1972	3.75	2.95	79	2.2	5.9	20
14 September 1972	4.1	3.5	85	2.0	6.1	25

Results

(1) Pulmonary function

The initial measurements made on 3 August 1972, while the patient was still taking sulphasalazine, and those made on 14 September 1972, 6 weeks after stopping the drug, are recorded in Table 1. The only significant difference between the two sets of values was in transfer factor, which was lower while the patient was on the drug, but lung volumes were also very slightly less at that time.

The patient gave informed consent to undergoing challenge tests. He was given 1 g of sulphasalazine on each of the mornings of 18 September 1972 and 19 September 1972. He felt a little unwell, though without fever, about 4 hr after the initial dose. Lung function tests were done at intervals after the second dose and are recorded in Table 2. A reduction in lung volumes and transfer factor was present up to 24 hr after the second dose, when the experiment had to be discontinued. It was noted that his basal inspiratory crackles had become more profuse through the 24 hr.

In order to determine whether the reaction was due to either the sulphonamide or salicylate component of sulphasalazine, a further challenge test was carried out using sulphapyridine. The patient was readmitted on 23 October 1972 and, after control measurements of lung function, was given 1 g of sulphapyridine at 8 a.m. on 24 October 1972. Thirty minutes later his temperature rose to 38.5°C and he appeared cyanosed. He was slightly breathless, though only sparse crackles were heard in his lungs. At this point lung function tests (Fig. 1) showed a marked fall in ventilatory

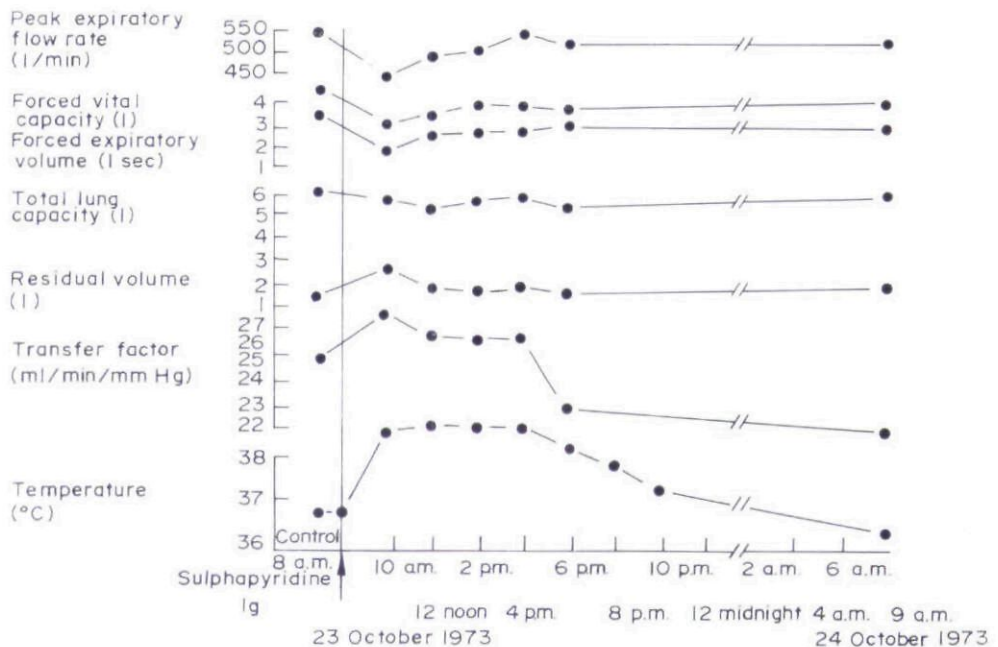
Table 2. Lung function tests before challenge and after two doses of 1 g sulphasalazine

Date	Vital capacity (litres)	Forced expiratory volume (1 sec) (litres)	FEV ₁ FVC %	Residual volume (litres)	Total lung capacity (litres)	Transfer factor (ml/min/mm Hg)
14 September 1972 (Control)	4.1	3.5	85	2.0	6.1	25
19 September 1972– 20 September 1972 3 hr after oral dose 1 g sulphasalazine	3.8	2.75	71	1.65	5.48	16
7 hr after	3.8	3.00	79	2.9	5.5	18
11 hr after	3.6	2.6	72	2.0	5.6	20
24 hr after	3.90	3.25	83	1.75	5.65	17

capacity with a rise in residual volume and a corresponding rise in transfer factor. There was also arterial hypoxaemia. Within 4 hr this obstructive lesion was improving and the patient felt much better. The transfer factor remained normal up to 10 hr after challenge, when it started to fall, and it was still reduced 24 hr after challenge. The patient remained febrile until 10 hr after the challenge. Again, for business reasons, the patient was unable to stay for any further testing.

(2) Immunological studies

(a) *Eosinophil counts before and during challenge.* The count before challenge with sulphapyridine was $77/\text{mm}^3$. Two and 6 hr after challenge the counts were 66 and 77 respectively and rose only to 160 at 24 hr.

**Fig. 1.** Serial lung function tests following challenge with 1 g sulphapyridine.

(b) *Skin tests.* An intradermal injection of a solution of sulphasalazine produced neither immediate nor delayed reactions.

(c) *Smooth muscle antibody was weakly positive.* DAT was positive at only 1 in 4 dilution. Gastric parietal cell, intrinsic factor, and thyroid antibodies were negative. No precipitating antibody was detected to *micropolyspora faeni*, *aspergillus fumigatus*, *candida albicans*, *bacillus subtilis*, *thermoactinomyces vulgaris*, the 'air conditioner pneumonitis' organism, and avian extracts.

(d) *Haemagglutinating antibody.* None of the patient's serum samples, obtained before and during the sulphasalazine challenge, had titres higher than control values.

(e) *Sulphasalazine-binding immunoglobulin.* No increased binding of sulphasalazine by the patient's serum was detected compared with control sera. All values were less than 4.5 μ g sulphasalazine-binding/ml serum.

(f) *Complement utilization.* Values obtained, expressed as CH₅₀ units/ml serum were 46 units, 14 hr prior to challenge, 62 units 2 and 6 hr after challenge, and 82 units 24 hr after challenge. Depletion of serum complement does not, therefore, appear to have been a feature of this patient's pulmonary response to sulphasalazine.

(g) *Sulphapyridine-binding immunoglobulin.* No binding values greater than 4.2 μ g sulphapyridine/ml serum were found in patient's or control sera.

(h) *Leucocyte migration inhibition.* At 5 μ g/ml sulphasalazine migration indices of 0.86 with the patient's leucocytes and 1.22 with the control leucocytes were obtained. However, no further inhibition occurred with the higher concentration of 50 μ g/ml sulphasalazine (migration indices of 0.86 with the patient's leucocytes and 1.03 with the control) while at 500 μ g/ml a toxic effect of the drug inhibited all migration. The results were interpreted as not indicating specific lymphocyte sensitization to sulphasalazine.

Discussion

Sulphasalazine, a compound of sulphapyridine and 5-amino salicylic acid, is widely used in the treatment of ulcerative colitis. It is absorbed mainly in the small intestine but its action on the colon is believed to be related to its affinity for connective tissue, the sulphonamide and salicylate components being released at the site of inflamed connective tissue around the colon (Svartz, 1968). The precise mode of action is unclear though both sulphonamides and salicylates have effects on antigen-antibody reactions in addition to their better known antibacterial and analgesic actions (Svartz, 1968). Both salicylates and sulphonamides may occasionally produce toxic effects on the lungs. Aspirin is well known as a cause of asthmatic reactions usually starting within 20 min of ingestion though later reactions up to 2 hr may occur (Samter & Beers, 1968). The precise immunological abnormality has not been demonstrated. Aspirin may also cause pulmonary eosinophilia (Ford, 1966). This has also been described following sulphonamides (Fiegenberg, Weiss & Kirshman, 1967). This syndrome presents with cough and the production of sputum containing eosinophils, and chest radiography reveals patchy alveolar infiltrates. There is usually blood eosinophilia. Histological studies in one case have shown alveolar exudation of eosinophils and histiocytes without appreciable interstitial involvement (Fiegenberg *et al.*, 1967). The reaction occurred 1 week after challenge with the drug but again the immunological mechanism was unclear. Sulphonamides have also been incriminated as a cause of polyarteritis nodosa (Symmers, 1958) and a syndrome resembling systemic lupus (Lee & Seigel, 1968).

We know of only one previous report of pulmonary reaction to sulphasalazine, even though the drug has been widely used since 1941. Jones & Malone (1972) described a patient, known to be aspirin sensitive, in whom the drug caused eosinophilia and pulmonary infiltration associated with cough, dyspnoea, and objective evidence of pulmonary dysfunction. Challenge with sulphasalazine caused initially some evidence of airways obstruction with lowered ventilatory capacity and increase in residual volume and after several days a progressive fall in transfer factor.

Our investigation of the functional abnormality following challenge with sulphasalazine demonstrated a change consistent with a reaction at the gas exchanging part of the lung, occurring within a few hours of taking the drug. The reaction to oral sulphapyridine was more dramatic, there being clear evidence of an early bronchial reaction associated with generalized malaise and fever, followed about 10 hr later by a reaction in the more peripheral parts of the lung, with a fall in gas transfer. The sulphonamide component of the sulphasalazine therefore appears to have been responsible for the illness in this patient's case and it appears to have had a general, possibly serum sickness, type of effect associated with separate immediate bronchial and late alveolar reactions. Such pulmonary reactions resemble a combination of the immediate hypersensitivity to inhaled or ingested allergens, combined with a late type 3 reaction such as occurs in extrinsic allergic alveolitis. As IgG-mediated reactions may produce immediate and late asthmatic reactions, as well as the better known allergic alveolitis (Pepys, 1973) it is tempting to speculate that the mechanism of sulphasalazine lung toxicity might be IgG-mediated. However, serum from our patient did not bind either sulphasalazine or sulphapyridine in greater amounts than control sera, neither was haemagglutinating activity nor serum complement utilization detected during challenge with sulphasalazine. Moreover, skin tests were negative.

Finally we investigated the possibility of cellular hypersensitivity to sulphasalazine by the leucocyte migration test, and once again this technique did not provide convincing evidence of a cell-mediated immune reaction.

Several possibilities may be suggested to explain the pulmonary lesions, if indeed the reaction is immunological in nature.

For example, immunoglobulin or lymphoid cells reacting with sulphasalazine or its breakdown products may form complexes with lung tissue or production of immunoglobulin may be localized to the lung and react *in situ*. Lung biopsy would be necessary to verify these suggestions. However, these would not explain the generalized febrile reaction to the sulphapyridine in our patient. The mechanisms of this drug's toxicity, therefore, remain obscure.

There has been increasing recognition of the association of autoimmune disease of the lung with that of other organs and there is at least one report of a patient with both ulcerative colitis and fibrosing alveolitis, in this case the pulmonary disease preceding the bowel symptoms (Turner-Warwick, 1968). It is quite possible that in future cases the pulmonary reaction to sulphasalazine could be mistaken for an acute form of fibrosing alveolitis and it is important to bear in mind the possibility of a drug reaction before attributing the two conditions to a common, possibly autoimmune, mechanism.

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