Agranulocytosis associated with sulphasalazine therapy

P. COCHRANE
M.D., M.R.C.P., D.C.H., D.R.C.O.G.

P. ATKINS
M.S., F.R.C.S.

S. EHSANULLAH
M.B., B.S., D.T.M.&H., D.C.P., D.Path.

Walton Hospital, Liverpool

Summary

A case report of a patient with agranulocytosis associated with sulphasalazine therapy is described. Recovery followed supportive therapy and withdrawal of the drug. Investigations including tests for leucocyte antibodies, the presence of which might have suggested an immunological cause for the drug reaction, were negative; an acetylation study, however, characterized the patient as a 'slow' acetylator phenotype, suggesting that the drug reaction was more likely to have been toxic in nature. It is suggested that acetylation studies be performed in patients who have previously shown serious side effects to sulphasalazine to assess the incidence of 'slow' acetylators.

Introduction

Sulphasalazine is now well established as an effective drug in the treatment of ulcerative colitis (Misiewicz *et al.*, 1965). Minor side effects are common; variously reported as between 9 and 60%—Collins, 1968 and Lennard-Jones *et al.*, 1960 noted that more than half of their patients receiving 4 g/day had anorexia, nausea and malaise. Serious haematological complications are uncommon and agranulocytosis is rare (Collins, 1968). The sulphapyridine component of sulphasalazine is thought to be responsible for the side effects. Two mechanisms have been postulated, either that the sulphapyridine has a direct toxic effect, or that it brings about an immunological response (Evans & Ford, 1958). Here we describe a case report of a patient who developed agranulocytosis following sulphasalazine and the investigations performed to elicit the nature of this drug reaction.

Case report

A 70-year-old female was first seen at Walton Hospital, Liverpool, on 1 February 1972, complaining of passing blood and mucus per rectum for 3 months. The faeces were loose and the bowels moved up to twenty times a day. She was otherwise well and her weight had remained steady. Her

previous history was unremarkable, apart from a history of contact eczema to rubber, flour and nickel. Sigmoidoscopy showed a granular mucosa with blood and mucus extending throughout the rectum and sigmoid colon, which was typical of ulcerative colitis. A biopsy taken at 20 cm showed a densely inflamed mucosa, compatible with ulcerative colitis. A barium enema on 24 February showed no abnormality. The haemoglobin, white cell count and film were normal at this time. Codeine phosphate 30 mg twice daily was prescribed initially, but as the diarrhoea persisted, sulphasalazine 1 g four times daily was started on 29 February. After taking three sulphasalazine tablets her eyes became swollen; she temporarily stopped this treatment and the swelling rapidly settled. When admitted for assessment on 13 March, her bowels were open four times per day and sigmoidoscopy showed some improvement, although a patchy granular proctocolitis was still present. Sulphasalazine was therefore restarted and there was no further swelling of her eyes.

The patient was seen on 18 April when the diarrhoea was well controlled, but she complained of anorexia, marked lassitude and weight loss. The sulphasalazine therapy was therefore stopped. These symptoms were associated with a neutropenia (WBC 1900/mm³), although this result was not known until she was admitted to hospital 6 days later. By this time she had developed a patchy pustular rash affecting the face and limbs. In addition she complained of rigors and abdominal cramps. On examination, she was dehydrated with a rapid tachycardia and a temperature of 101.2°F. Investigations performed at this time showed that the white cell count had fallen to 900/mm³—made up entirely of lymphocytes and monocytes. The haemoglobin was 10 g/100 ml and the platelet count was normal. *Escherichia coli* were cultured from the blood and *Staphylococcus aureus* from the skin pustules. Examination of the bone marrow showed large numbers of myelocytes and metamyelocytes, but no mature granulocytes ('maturation arrest')—red cell

formation was normal (Fig. 1). Vigorous treatment was instituted; this included gentamycin (60 mg i.v., 8 hourly), cloxacillin (500 mg i.v., 6 hourly), hydrocortisone (100 mg i.v., 6 hourly) and γ globulin (500 mg i.m. *Stat.*). Over the next few days the patient's condition improved dramatically and the blood count returned to normal (Fig. 2). Later, two abscesses on the nose and one on the right leg were incised, but otherwise the patient made an uneventful recovery. A second bone marrow examination on 9 May was entirely normal. In addition to the regular blood counts, the following investigations were also performed at this stage. Coombs' test, negative; serum bilirubin, 1.0 mg/100 ml; reticulocyte count, 1%; urinary urobilinogen, no excess; Heinz body test, negative; serum folate, 5.2 mg/100 ml; vitamin B₁₂, 1200 μ g/100 ml; serum iron, 72 μ g/100 ml; total iron binding capacity, 330 μ g/100 ml; % saturation, 22%; RA and LE latex, negative; ANF, negative; blood urea, 26 mg/100 ml; serum sodium, 127 mEq/l; serum chloride, 102 mEq/l; and serum potassium, 3.1 mEq/l. Total plasma proteins, 6.3 g/100 ml; albumen, 3.0 g/100 ml; total globulin, 3.3 g/100 ml; α_1 globulin, 0.3 g/100 ml; α_2 globulin, 0.9 g/100 ml; β globulin, 1.0 g/100 ml; and γ globulin, 1.1 g/100 ml.

Three days later a screening test for cytotoxic (Terasuki & McClennand, 1964) and leucoagglutinat-

FIG. 1. Sternal marrow of patient with agranulocytosis associated with sulphasalazine therapy, showing excess myeloid precursors ('maturation arrest') but no mature polymorphs. Red cell formation is normal.

ing antibodies (Walford, 1960) was negative. Subsequently, after recovery of the white cell count, an isoniazid acetylation test (Evans & White, 1964) was performed; this characterized the patient as a 'slow' phenotype. (The patient was fasted for 12 hr; at 6 a.m. a single dose of isoniazid was taken. The blood levels of isoniazid were: 8 a.m., 13.24 µg/ml;

FIG. 2. Haematological parameters in a patient with agranulocytosis associated with sulphasalazine therapy.

10 a.m., 7.34 µg/ml; 12 noon, 4.32 µg/ml; $\frac{1}{2}$ life ($T_{\frac{1}{2}}$) = 2.58 hr. Both intradermal and prick tests with a solution of sulphasalazine were negative. Protein immunophoresis showed a slightly raised IgA and a low IgM—IgG, 1150 mg/100 ml; IgA, 400 mg/100 ml; IgM, 55 mg/100 ml; IgD, < 5 mg/100 ml.

Discussion

In the assessment of severe drug reactions, one has to rely on probabilities that a particular drug is responsible, for definite proof requires re-challenging the patient with the drug, a procedure which is fraught with danger. It seems likely that sulphasalazine was responsible for the transient agranulocytosis described in this case report, as rapid recovery followed supportive therapy and withdrawal of the drug.

Agranulocytosis is a rare complication of sulphasalazine therapy, and up to 1968 only twenty cases had been recorded in the literature (Collins, 1968). In the present case the bone marrow feature of 'maturation arrest' presumably reflected a recovery phase. This appearance is believed to indicate a better prognosis than the finding of an aplastic marrow (De Gruchy, 1970). Previous reports showing a high mortality underline the seriousness of infection in these patients, and this was a feature of the present case.

The most frequent haematological complication of sulphasalazine therapy is Heinz body formation, which occurs in 8% of the patients treated with the drug (Bottinger *et al.*, 1963), but Heinz body haemolytic anaemia and non-Heinz body haemolysis may rarely occur (Gardner & Borgen, 1964). Although there was a slight fall in haemoglobin in the present case, no evidence of haemolysis was apparent. Thrombocytopenia (Thirkettle, Gough & Read, 1963), methaemoglobinemia and sulphaemoglobinemia (Gardner & Borgen, 1964) have also been noted with sulphasalazine treatment.

The mechanism of sulphasalazine induced agranulocytosis is uncertain. After absorption from the gut, sulphasalazine is deposited in connective tissue, where aminosalicilic acid and sulphapyridine are released. Sulphapyridine has long been recognized as one of the most toxic of the sulphonamides. It is possible that this toxic metabolite may cause agranulocytosis, either by depressing the production of granulocytes, or by increasing their peripheral destruction (Evans & Ford, 1958). These workers studied a case of agranulocytosis associated with sulphasalazine therapy and concluded that an immune mechanism was responsible for the depression in production of granulocytes, for they demonstrated transient white cell agglutinins in the serum. In the present case, however, the absence of leucocyte antibodies, negative sulphasalazine skin tests and

the minimal changes in protein immunophoresis would all argue against an immunological cause for the agranulocytosis. On the other hand, the patient was shown to be a 'slow' acetylator, and it is known that such individuals tend to have higher blood levels of the drug and suffer a greater incidence of minor side effects (Schroeder & Evans, 1972). Thus a 'toxic' cause for the agranulocytosis seems more likely.

It would be of considerable interest to ascertain the acetylator status of patients who have had severe reactions to sulphasalazine. This information might be valuable in assessing the likelihood of patients with minor reactions subsequently suffering major complications.

This case has been reported to the Committee on Safety of Medicines.

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