Neutropenia in patients with inflammatory arthritis treated with sulphasalazine

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SUMMARY   This report describes two patients who developed severe neutropenia one month after starting sulphasalazine (SASP) as treatment for their inflammatory joint disease. Both recovered on stopping the drug. Six further cases (out of a series of 180 patients with inflammatory forms of arthritis receiving SASP therapy) in whom transient leucopenia occurred are also recorded. These patients were able to continue the drug under close supervision. Sulphasalazine is a useful addition to the small number of slow acting antirheumatic drugs (SAARDs) and, despite this complication, is safer than other SAARDs. Careful monitoring of patients is essential, however, particularly in the early stages of treatment, to detect this adverse reversible reaction promptly.

Sulphasalazine is now becoming established as a slow acting antirheumatic drug. Short term clinical trials and long term open studies have shown that it is of benefit in the treatment of rheumatoid arthritis (RA).[1-6] Recently Bax and Amos have stated that it is a safe drug for prolonged therapy.[6] This report describes two patients who were treated with sulphasalazine to control their active inflammatory arthritis and who developed severe neutropenia necessitating withdrawal of the drug. These two cases are compared with those of six others who developed transient leucopenia during treatment with SASP but who continued therapy under careful supervision. The eight patients reported are part of a study to evaluate the use of SASP in 180 patients with inflammatory forms of arthritis (150 with RA and 30 with seronegative inflammatory arthritides).

Case reports

PATIENT 1
A 43 year old man with a 19 year history of ankylosing spondylitis (with iritis and peripheral joint involvement) was treated with sulphasalazine to control his active joint disease. He had not previously received any second line agents. One month before receiving SASP he was started on 20 mg prednisone for iritis and was now on a decreasing

regimen. He was taking indomethacin, which he had received for the last 11 years.

He was treated with enteric coated SASP 500 mg daily for one week, increasing to 2 g daily over a period of one month. He continued indomethacin and also received a course of intramuscular iron injections. After taking sulphasalazine for one month his joints had improved in spite of steroid withdrawal, but he developed severe neutropenia (neutrophil count $<0.2 \times 10^9$/l). SASP and indomethacin were both stopped, but the latter was restarted after four days because of incapacitating stiffness. The neutropenia responded rapidly to stopping SASP and within one week the leucocyte and neutrophil counts were normal (Fig. 1). Bone marrow examination did not show any depression of granulopoiesis. His neutropenia was therefore interpreted as a probable peripheral consumption, perhaps related to anti-white cell antibodies induced by previous exposure to sulphonamides.

PATIENT 2
A 63 year old man with an eight year history of seropositive, erosive, nodular rheumatoid arthritis with pulmonary involvement was treated with sulphasalazine to control his active joint disease. He was also being treated for mild hypertension with nifedipine and for angina with glyceryl trinitrate when required. He had not previously received any other second line drugs for his RA but had been treated with a small dose of prednisolone (5 mg) for
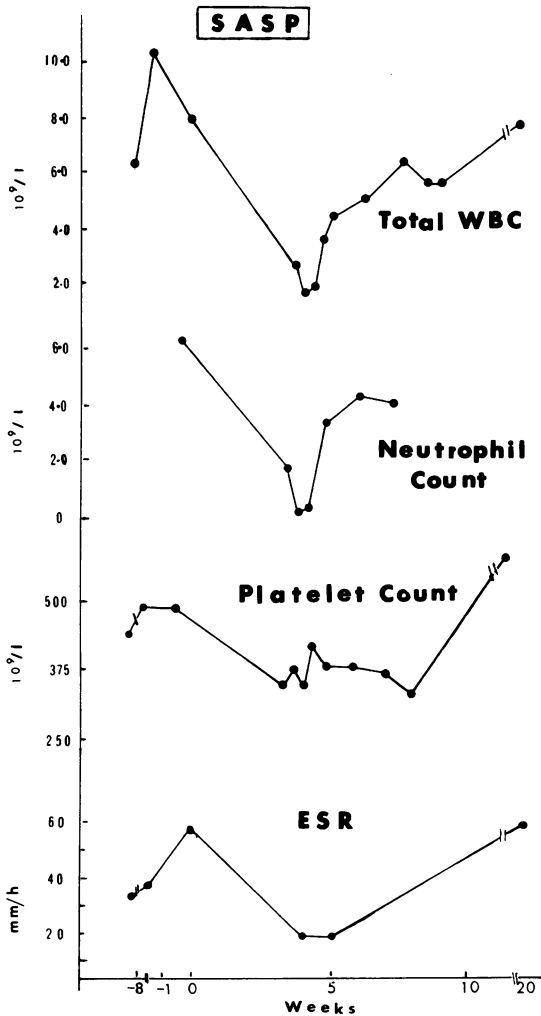
Fig. 1 Changes in total white cell (WBC), neutrophil, and platelet counts and the erythrocyte sedimentation rate (ESR) in patient 1 during treatment with sulphasalazine.

12 months when his arthritis began, and again two years later to control pleurisy associated with his RA. He was currently taking only mefenamic acid for his arthritis. His haemoglobin (Hb) was 14·3 g/dl, (143 g/l), ESR 44 mm/1st h, white blood cell count (WBC) $5·81 \times 10^9/l$, and platelet count $220 \times 10^9/l$ (Fig. 2).

He was started on 500 mg enteric coated SASP daily. He became nauseated and lightheaded, but this settled after three weeks and the dose of SASP was increased to 1·5 g daily. One week later he developed acute neutropenia. WBC was $2·78 \times 10^9/l$

and neutrophil count $0·7 \times 10^9/l$. Platelet count remained normal ($225 \times 10^9/l$), Hb was 13·9 g/dl (139 g/l), ESR had fallen to 24 mm/1st h, and his joints had improved.

Sulphasalazine was stopped, and the neutrophil count returned to normal over five days. Bone marrow examination showed a cellular picture with active granulopoiesis but paucity of mature forms. Ponstan was continued throughout the time reported.
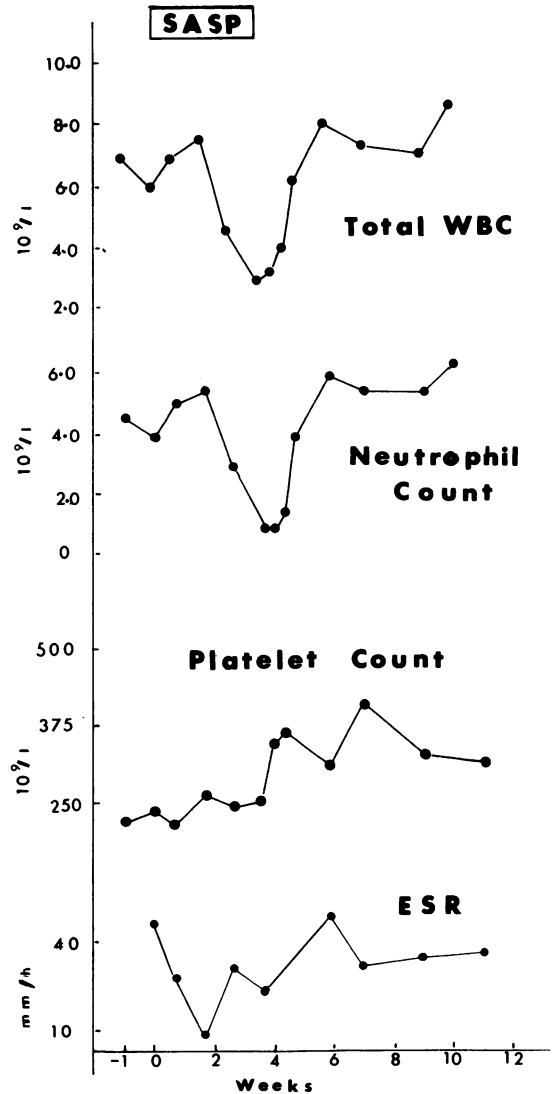

Fig. 2 Changes in total white cell, neutrophil, and platelet counts and the erythrocyte sedimentation rate in patient 2 during treatment with sulphasalazine.

Table 1 *Details of patients 3–8 who developed transient leucopenia during SASP therapy*

Patient No	Form of arthritis	Duration of SASP (months)	Duration of leucopenia (months)	White cell count $\times 10^{-9}/l$	Neutrophil count $\times 10^{-9}/l$	ESR (mm/1st h)	Management
3	RA	12	3	5·1→3·4	4·12→2·73	21	Dose continued
4	RA	2	16	5·9→3·2	→1·39	2	Dose reduced
5	Seronegative polyarthritis	9	2	4·9→3·5	2·31→1·77	10	Dose continued
6	RA	18	2	6·5→3·5	→2·1	10	Dose continued
7	SLE*/ RA/Sjögren's	2	6	4·1→2·8	→1·78	50	Temporary withdrawal
8	Seronegative polyarthritis	1	4	6·7→3·4	3·34→1·4	13	Dose reduced

*SLE=Systemic lupus erythematosus.

PATIENTS 3–8 (Table 1)
Six further patients (out of 180 receiving SASP for treatment of inflammatory arthritis) also developed leucopenia. In three patients the fall in total white cell count occurred within two months of starting therapy, whereas the other three patients developed leucopenia between nine and 18 months. The drug was temporarily withdrawn in patient 7 and restarted and maintained at a lower dose (1 g daily). In patients 4 and 8 the dose was reduced from 2 g to 1·5 g daily, and in patients 3, 5, and 6 the drug was continued at the original dose of 1·5 g daily. All patients responded to the drug both clinically and by a reduction in their serological parameters of disease activity.

Discussion

Sulphasalazine is an effective, slow acting drug for the treatment of RA, but its use as a second line agent will be influenced by the frequency and nature of its adverse reactions.

All the patients in this study had acute inflammatory joint disease and had a good response to SASP shown both clinically and by an improvement in their serological parameters. After one month of therapy with SASP, however, patients 1 and 2 developed acute neutropenia, which resolved after stopping the drug. In patient 1 the bone marrow did not show any depression, and this was interpreted as a probable peripheral consumption perhaps related to white cell antibodies induced by a previous exposure to sulphonamides. The bone marrow of patient 2 again showed a cellular picture consistent with 'maturation arrest'. Pullar *et al* also reported leucopenia occurring early in treatment in each case.[7] In our six patients who developed transient leucopenia it occurred in three of them within two months of starting treatment, but in the other three it developed after nine months, one year, and 18

months of treatment respectively. Neutropenia has been reported after three years of therapy in a patient with inflammatory bowel disease but again rapidly resolved when SASP was discontinued. In this case the patient once more developed neutropenia when the drug was restarted (West Midlands Centre of Adverse Drug Reactions Reporting, personal communication). In our series all patients with mild leucopenia were able to continue therapy with SASP, though the drug was temporarily withdrawn in one patient and restarted at a lower dose, and in two other patients the dose was reduced.

Sulphasalazine has been used to treat inflammatory bowel disease for 45 years and its effects on the haemopoietic system have been described.[8] Neutropenia and agranulocytosis are rare complications but probably the most serious. Less than 30 cases had been reported up to 1979, but at least five deaths had occurred.[9] As yet there are little data on the toxicity of the drug in RA. In the limited number of long term studies carried out comparatively few serious haematological side effects have been reported. The most common is megaloblastic anaemia.[1 4] Our own initial study[4] and those of other workers have shown that the total white cell count is significantly reduced in RA patients treated with SASP but does not usually fall below the lower end of the normal range. This was thought to reflect improvement in disease activity rather than a drug effect on the bone marrow. McConkey *et al* from his large experience of the drug first reported one case of neutropenia.[1] Pullar *et al* described seven patients out of a total of 158 RA patients treated with SASP who developed leucopenia (two severe) all within the first 10 weeks of therapy.[7] All recovered with conservative management. This report is consistent with our own series, in which eight out of 180 patients developed leucopenia, two of which were severe. Both the reported Glasgow and Birmingham University figures provide an incidence of 4·4%

approximately, suggesting that this complication is more common in RA than in inflammatory bowel disease. This accords with other evidence that the disease state contributes to the frequency of drug related side effects in RA.

Sulphasalazine is a useful addition to the small number of second line drugs and despite the complications reported, the drug still has a better safety profile than other second line drugs. The neutropenia does appear to be completely reversible if SASP is stopped soon enough. Our policy based on these observations is to monitor therapy particularly carefully during the first 12 weeks but to continue long term monitoring throughout dosage of the drug.

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