Sulphasalazine in ankylosing spondylitis

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SUMMARY   In recent years sulphasalazine has gained acceptance as an effective agent for the treatment of rheumatoid arthritis. Ankylosing spondylitis is a disease where remission inducing drugs so far have been lacking. In this double blind trial sulphasalazine was compared with placebo in 37 patients with ankylosing spondylitis. Evaluation after three months' treatment showed reduction of inflammatory activity and improvement of clinical variables. The side effects were mild. The results suggest that sulphasalazine is a potentially effective and safe drug in the treatment of ankylosing spondylitis.

Key words: haptoglobin, orosomucoid, side effects.

Although in the early forties sulphasalazine (SASP) was suggested as an antirheumatic drug in relation to contemporary theories of an influence on rheumatic diseases by intestinal bacterial infections,[1] it was not accepted as an agent effective in rheumatoid arthritis but rather as the drug of choice in the treatment of ulcerative colitis.[2] Not until recently has SASP gained a position as a second line antirheumatic drug, mainly through the works of McConkey and coworkers.[3] So far the studies on SASP and rheumatic disease have dealt only with rheumatoid arthritis, but in open studies we have also observed beneficial clinical effects in ankylosing spondylitis (AS).

The mechanism by which SASP reduces the inflammatory activity in rheumatic diseases remains unknown. A documented anti-inflammatory effect of SASP in AS, however, might support the original theory of an intestinal mode of action of the drug, considering the importance of intestinal bacterial infections in other HLA-B27 associated arthritic lesions.[4]

In the present controlled, double blind study we confirm our preliminary results with SASP in AS and suggest this agent as a therapeutic alternative in this disease.

Patients and methods

The patients were recruited from consecutive out-

patients suffering from definite AS according to the American Rheumatism Association criteria.[5] Patients who were HLA-B27 positive, with erythrocyte sedimentation rate (ESR) > 30 mm/1st h, raised haptoglobin ($\geqslant 2 \cdot 0$ g/l), or raised orosomucoid ($\geqslant 1 \cdot 2$ g/l) were included in the trial. All patients had morning stiffness for > 30 min or disturbed sleep due to pain or stiffness. The study met the ethical standards described in the Declaration of Helsinki.

Excluded from the study were patients with a history of inflammatory bowel disease, Reiter's disease, or psoriasis, and patients with a chronic infection, malignancy, or other concomitant illness which might interfere with the completion of the study. Known allergy or intolerance to sulphonamide or salicylates was also an exclusion criterion, as was significant renal, hepatic, or haematological disease.

Patients fulfilling the criteria for the study were randomly allocated to receive active or placebo treatment. The patients were given one study tablet (Salazopyrin EN 0·5 g) twice daily for the first week. The dose was then increased by one to two tablets weekly on an individual basis to a maximum of six tablets or 3 g a day or the highest dose the individual patient could tolerate. The treatment period was 12 weeks. The patients were allowed a non-steroidal anti-inflammatory drug (NSAID) as a pain reliever.

The disease activity was assessed by clinical parameters: duration of morning stiffness in minutes; severity of stiffness on a visual analogue scale (VAS), with the endpoint no stiffness at 0 mm and maximum stiffness at 100 mm; severity of pain on a VAS, with the endpoint no pain at 0 mm and

maximum pain at 100 mm; general wellbeing on a VAS, with very well at 0 mm and very ill at 100 mm; chest expansion (fourth intercostal space); Schober's test; number of painful joints, excluding lumbar spine, pelvis, and hips; number of swollen joints; sleep disturbance (yes or no) due to pain or stiffness; sacroiliac pain; and by laboratory parameters (haptoglobin, orosomucoid, and ESR). To evaluate safety the following parameters were measured at three and six weeks: haemoglobin, full blood count, serum creatinine, aminotransferases, and urine analysis (albumin and red blood cells). The patients were informed in writing of possible side effects and were given a chart on which to fill in the time and type of possible side effects. The measures taken were also noted, e.g., dose reduction, etc.

STATISTICS
The differences between the individual pretreatment and treatment values were calculated for each group and tested by Student's paired t test. The comparison between the treatment and the control group was made by Student's unpaired t test. A p value <0.05 was considered to be statistically significant.

Results

Table 1 summarises the pretreatment clinical and

Table 1 *Patient characteristics at start of study*

	Placebo	Sulphasalazine
Sex (♀/♂)	4/15	5/13
Age (years)	36·5 (19–57)*	41·3 (25–57)
Disease duration (years)	10·4 (2–20)	12·1 (2–30)
ESR (mm/1st h)	28·5 (19·5)	24·3 (17·4)
Haptoglobin (g/l)	2·91 (0·67)	2·94 (0·96)
Orosomucoid (g/l)	1·34 (0·32)	1·42 (0·49)
Morning stiffness (min)	72·6 (48·5)	64·2 (55·8)
Chest expansion (mm)	26·6 (12·8)	23·9 (10·6)
Schober's test (mm)	19·5 (14·4)	21·1 (10·2)

*Values are the mean with actual ranges or SD.

laboratory variables of the Salazopyrin and placebo groups. No statistical differences in these variables were noted.

Of the 37 patients enrolled in the study, 19 (51%) were given placebo and 18 (49%) active treatment with Salazopyrin EN. Altogether 29 patients completed the treatment; four in the placebo group and four in the group receiving active treatment did not complete the treatment. The reasons for stopping treatment were, in the placebo group, lack of effect (one patient), nausea (two), and rash (one), and, in the SASP group, rash and fever (two), rash and nausea (one), and rash solely (one). Side effects reported among those who completed the study
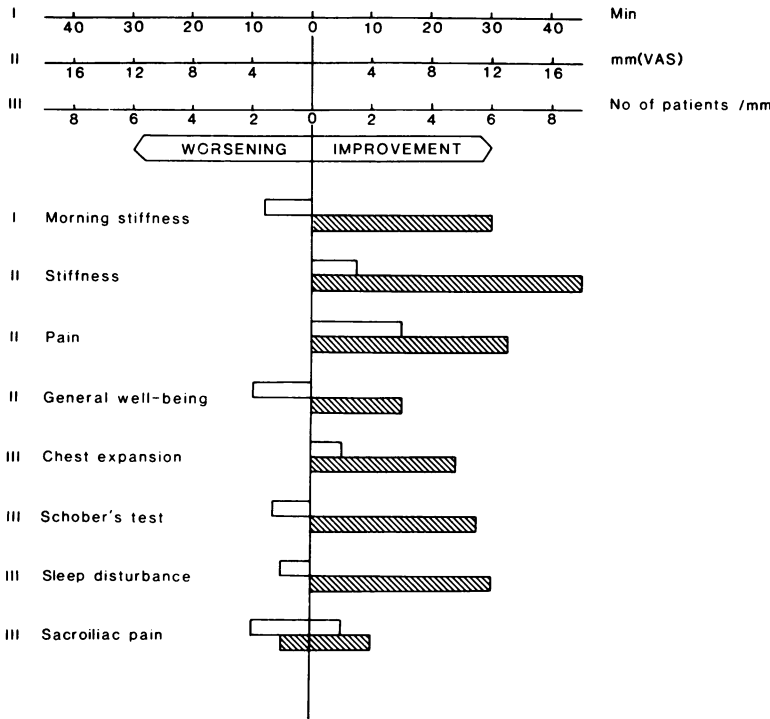

Fig. 1 *Improvement/worsening of clinical symptoms and signs in placebo (□) and Salazopyrin (▨) treated patients.*

were all mild, of the gastrointestinal type, and seemed dose dependent (SASP n=5, placebo n=3).

Of the clinical variables studied, stiffness (VAS), chest expansion, and degree of sleep disturbance showed significant improvement in the group with active treatment (Fig. 1). These patients also improved in all other variables, but the changes did not reach statistical significance. Minor improvement or worsening of the disease was observed in the placebo group (Fig. 1), with no significant improvement in any variable. The disease activity reflected by peripheral joint involvement was low in these patients. Only one out of 13 in the placebo group and one out of 14 in the SASP group suffered from peripheral synovitis. At the end of the study we found in the SASP treated group a decrease of ESR from 24·3±17·4 (SD) to 23·1±17·6 (NS),

haptoglobin from 2·94±0·96 to 2·14±0·93 (p>0·001), and orosomucoid from 1·42±0·49 to 1·26±0·48 (p~0·12). The individual changes of the acute phase plasma proteins are illustrated in Fig. 2. In the placebo group no changes of these variables were observed (Table 2). There was no significant difference between the effects on the clinical variables in the SASP and placebo groups except for diminished sleep disturbance in the SASP group (p<0·02, Fisher's exact t test). The inflammatory activity defined by haptoglobin and orosomucoid was significantly improved (p<0·001 and <0·05 respectively) in the SASP group compared with the placebo group (Table 2). Analysis of individual values in the SASP group showed the greatest improvement in the patients with an ESR >20 mm/h or haptoglobin >3·8 g/l.
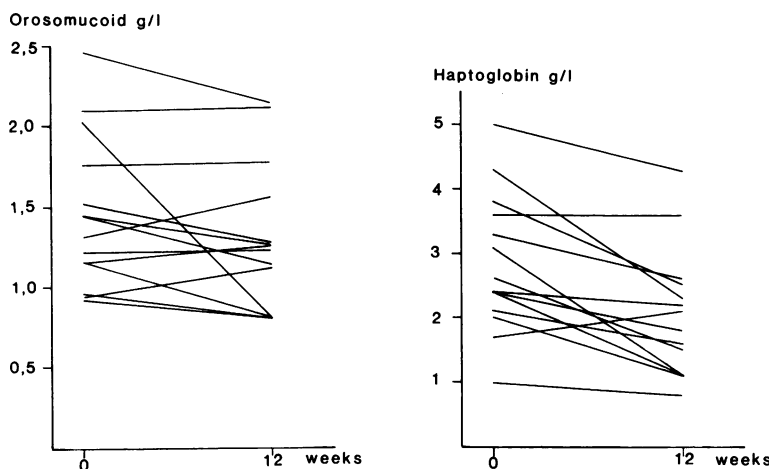

Fig. 2 *The individual haptoglobin and orosomucoid levels before and after Salazopyrin treatment.*

Table 2 *Laboratory evaluation*

	Pretreatment			After 12 weeks		Diff (12–0 weeks)				Between treatments	
	n	Mean	SD	Mean	SD	Mean	SD_d	t	p	t	p
Haptoglobin (g/l)											
Placebo	15	2·91	0·67	2·95	0·64	0·06	0·44	0·50	NS	3·82	<0·001
Salazopyrin EN	14	2·94	0·96	2·14	0·93	−0·80	0·69	4·33	<0·001		
Orosomucoid (g/l)											
Placebo	15	1·34	0·32	1·48	0·46	0·12	0·24	1·73	NS (p~0·1)	2·34	<0·05
Salazopyrin EN	14	1·42	0·49	1·26	0·48	−0·16	0·36	1·69	NS (p~0·12)		
ESR (mm/1st h)											
Placebo	15	28·5	19·5	25·1	13·2	−3·5	17·0	0·79	NS		NS
Salazopyrin EN	14	24·3	17·4	23·1	17·6	−2·2	9·5	0·82	NS		

NS=p>0·05.

Discussion

This study has shown the beneficial effects of SASP treatment in AS. It is the first study, to our knowledge, where a non-steroidal drug has improved both clinical and laboratory variables in AS, a disease where the use of remission inducing drugs so far has been lacking. The onset of clinical effects seems fairly similar to that reported in rheumatoid arthritis.[6] The improvement is usually obvious after eight weeks, so in most cases a 12 week test period should be sufficient. The side effects, as in RA, are mostly of the gastrointestinal type and mild. In our study we saw only one case of moderately severe allergic reaction. The side effects appear to be dose dependent, and we therefore recommend individualised dosage in future studies. No change in ESR was observed. The effect on the acute phase reaction defined by more sensitive variables (haptoglobin and orosomucoid) seems clear, though somewhat weaker than in rheumatoid arthritis. We do not interpret this as an effect of the prostaglandin inhibiting effects which have been ascribed to SASP, but as a possibly weak immunomodulatory mechanism of the drug.[7] The effects on stiffness, pain, and sleep disturbance may be attributed to an effect similar to that of NSAIDs.[8] [9]

We find the results in our study promising and take them as an indication of a possible alternative treatment in AS. Our experiences from open studies that SASP has the best effect in patients with inflammatory active disease is partly supported by this study.

The pathophysiological mechanisms in AS are still inadequately known. In reactive arthritis an associated infection in the gut, the urinary tract, or elsewhere is often present, but this is seldom evident in AS. There are theories that intestinal bacterial pathogens may influence the clinical course of AS.[10] In a genetically predisposed individual this may be due to either a direct effect of the viable bacteria or to an inadequate immune response to bacterial antigenic components, circulating immune complexes, or toxins.[11] In this context a possible mode of action of SASP could be a local effect on the intestinal bacterial flora or a modulation of the intestinal immune system.[12] [13]

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