between radiographic changes and the sedimentation rate and serum C reactive protein value—that when a drug induces clinical improvement as well as falls in sedimentation rate and C reactive protein it is likely to delay the rate of tissue damage in rheumatoid arthritis.[12-14] If this hypothesis is correct it implies that sulphasalazine belongs to the group of drugs that are used when the disease is not adequately controlled by non-steroidal anti-inflammatory agents. The best known members of this group are gold and penicillamine. Others are antimalarials, antiproliferatives, and perhaps dapsone. To select a drug from this group we must consider both efficacy and toxicity. Gold and penicillamine are of proved efficacy but have some serious adverse effects; antimalarials, antiproliferatives, and dapsone have not been shown to be better. In contrast, we found in this and our earlier studies[4-6]—in which we gave sulphasalazine to a total of 121 patients with rheumatoid arthritis—that adverse effects, though frequent, were never dangerous. The record of sulphasalazine in ulcerative colitis, too, suggests that it is safe, although reversible male infertility may occur.[15] If further trials yield similar results the safety record of sulphasalazine will make it the first choice remission inducing drug in rheumatoid arthritis.

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Sulphasalazine in rheumatoid arthritis: a double blind comparison of sulphasalazine with placebo and sodium aurothiomalate

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Abstract

Uncontrolled studies have suggested that sulphasalazine may be an effective second line agent in rheumatoid arthritis. Sulphasalazine was therefore compared with placebo and intramuscular sodium aurothiomalate in 90 patients with active rheumatoid arthritis. After six months' treatment both sulphasalazine and sodium aurothiomalate had produced significant clinical and laboratory benefit, whereas placebo had produced no significant change in any variable. Thirteen patients stopped taking the placebo because of lack of effect whereas only two patients stopped taking sulphasalazine and one sodium aurothiomalate for this reason. The major toxicity encountered in the group treated with sulphasalazine was nausea or vomiting, or both; this may be related to slow acetylator phenotype.

Sulphasalazine appears to be an effective second line agent, and further pharmacokinetic studies might prove useful in diminishing gastrointestinal side effects.

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Introduction

Sulphasalazine (4-pyridyl-(2)-aminosulphonyl-3-carboxy-4-hydrobenzol) was introduced by Svartz in 1942 for the treatment of rheumatoid arthritis and ulcerative colitis.[1] Despite further promising studies[2 3] the drug fell out of favour for the treatment of rheumatoid arthritis after the publication of Sinclair and Duthie's paper in 1948.[4] It was not until 30 years later that McConkey *et al* reported an open study of sulphasalazine in the treatment of rheumatoid arthritis,[5 6] and interest has again developed in the use of the drug for this condition. Bird *et al* recently screened the drug for "second line" properties and found it to have such qualities.[7]

To date no placebo controlled studies of sulphasalazine in

rheumatoid arthritis have been reported. We therefore carried out a placebo controlled study of sulphasalazine and intramuscular sodium aurothiomalate in the treatment of rheumatoid arthritis.

Patients and methods

Ninety patients with definite or classical rheumatoid arthritis,[8] whose active disease was not adequately controlled by non-steroidal anti-inflammatory drugs, were randomly allocated to receive sulphasalazine (enteric coated tablets (Salazopyrin)), sodium aurothiomalate, or sulphasalazine placebo (30 patients in each group). Patients receiving tablets were unaware of whether they were receiving sulphasalazine or placebo, as were their doctors. The nurse carrying out subjective and semiobjective measurements was similarly unaware of the nature of the treatment. Non-steroidal anti-inflammatory drugs were continued in all patients, and no patients received corticosteroids during or in the three months preceding the study. Patients were excluded if they were known to be sensitive to sulphonamides. Sulphasalazine was given in an initial dose of 0·5 g/day, and this was increased weekly by increments of 0·5 g/day to a maximum dose of 3 g/day. Sulphasalazine placebo tablets were administered in the same pattern. After a 10 mg test dose 50 mg sodium aurothiomalate was administered intramuscularly weekly to a maximum total of 1 g or until a clinical response had been obtained. Thereafter the frequency of injections was reduced to the minimum necessary to maintain the clinical response. Disease activity was assessed at weeks 0, 6, 12, 18, and 24 by both clinical variables (Ritchie articular index, pain score, hand grip strength, and limbering up time) and laboratory variables (erythrocyte sedimentation rate, haemoglobin concentrations, platelet count, and rheumatoid factor titre). Urea and electrolyte concentrations and results of liver function tests were also assessed at intervals of six weeks. In the patients treated with sodium aurothiomalate full blood count and urine analysis were carried out at the time of each injection.

Treatment was stopped if a potentially serious adverse effect became apparent or if a patient felt unable to continue treatment because of side effects. Every attempt was made to discourage patients from stopping treatment because of lack of efficacy before the assessment at 24 weeks.

TABLE I—*Patient characteristics at start of study (median values (and ranges))*

	Placebo	Sulphasalazine	Sodium aurothiomalate
Age (years)	56·5 (18-70)	57 (32-70)	58 (40-74)
Duration of disease (years)	9·5 (1-35)	6 (1-23)	8 (1-32)
Erythrocyte sedimentation rate (mm in 1st h)	47 (4-128)	65 (15-131)	48 (8-119)
Haemoglobin (g/dl)	12·7 (8·6-14·7)	11·1 (9·4-14·2)	11·8 (8·8-15)
Platelets ($\times 10^9$/l)	407 (250-586)	438 (259-786)	398 (276-817)
Rheumatoid factor titre	1/64 (0-1/1024)	1/32 (0-1/1024)	1/64 (0-1/1024)
Articular index	18 (6-40)	22 (2-54)	18 (5-33)
Limbering up time (min)	60 (0-all day)	120 (0-all day)	60 (0-all day)
Pain score	2 (0-4)	3 (0-4)	2 (0-4)
Grip strength (mm Hg)	84 (49-225)	83 (40-160)	90 (52-136)
Index of disease activity	2·50	2·84	2·67

Acetylator state was assessed by measuring the ratio of urinary free sulphapyridine to acetyl sulphapyridine as described by Schröder.[9] In patients who had stopped sulphasalazine treatment before urine could be collected acetylator state was assessed after a dose of sulphadimidine 10 mg/kg, as described by Evans and White.[10]

Statistical analysis was carried out using non-parametric statistics. In addition to individual variables of disease activity a disease activity index was calculated, as described by Mallya and Mace.[11] This was slightly modified, however, in that the data were expressed as a "raw score"—that is, the mean sum of the six individual variables —rather than in the final grading of I to IV.

Results

Table I shows the characteristics of the patients at the start of the study. There was no significant difference in these characteristics between the groups (Kruskal-Wallis: $p > 0.05$).

After 12 weeks 25 patients were still taking sodium aurothiomalate, 22 sulphasalazine, and 24 placebo. After 24 weeks 18 patients were still taking sulphasalazine, 18 sodium aurothiomalate, and 14 placebo. The main reasons given for stopping treatment were lack of effect (placebo 13 patients, sulphasalazine two, and sodium aurothiomalate one) and adverse effects (placebo two patients, sulphasalazine nine, and sodium aurothiomalate 11); other reasons were given by one patient taking placebo and one taking sulphasalazine. Table II gives the times of and exact reasons for stopping treatment. One patient developed agranulocytosis after nine weeks of treatment with sulphasalazine. The white cell count fell to $0{\cdot}5 \times 10^9$/l (differential: polymorphs $< 10\%$); she was managed conservatively in hospital, and the white cell count rose to $10{\cdot}9 \times 10^9$/l after five days.

The analysis of disease activity included those patients who had stopped treatment at the 24 week visit (since 24 week data were available for those patients). Erythrocyte sedimentation rate at 0, 6, and 12 weeks and all clinical and laboratory variables of disease activity at 0 and 24 weeks were compared (Wilcoxon matched pairs signed rank test). After six weeks of treatment there was no significant improvement in the erythrocyte sedimentation rate in any of the groups ($p > 0.05$), whereas after 12 weeks it had improved in the group taking sodium aurothiomalate ($p < 0.02$) but not in the groups taking sulphasalazine or placebo ($p > 0.05$). No significant improvement was seen in patients treated with placebo in any of the variables of inflammation at 24 weeks whereas patients treated with sulphasalazine showed improvement in the erythrocyte sedimentation rate, platelet count, articular index, grip strength, and disease activity index, and patients treated with sodium aurothiomalate showed improvement in the erythrocyte sedimentation rate, rheumatoid factor titre, articular index, pain score, and disease activity index (table III).

There was no significant difference between any of the three groups in inflammatory variables at week 24 or in the degree of change in these variables over the treatment period (Kruskal-Wallis: $p > 0.05$).

Acetylator state was assessed in 28 of the patients treated with sulphasalazine: 15 were slow acetylators and 13 fast acetylators. Five of the six patients who stopped taking sulphasalazine because of gastrointestinal intolerance were slow acetylators, whereas both patients who stopped because of lack of effect were fast acetylators.

TABLE II—*Time and cause of stopping treatment (0-24 weeks)*

	Placebo		Sulphasalazine		Sodium aurothiomalate	
	No of patients	Week stopped	No of patients	Week stopped	No of patients	Week stopped
Rash	0		1	4	4	16, 18, 22, 24
Mouth ulcers	0		1	2	2	10, 12
Fall in platelet count	0		0		2	16, 20
Fall in white cell count	0		1	9	1	12
Nitritoid reaction	0		0		1	2
Proteinuria	0		0		1	10
Nausea or vomiting	2	6, 8	6	5, 6, 6, 12 13, 20	0	
Lack of effect	13	6, 12, 12, 16, 18, 18, 18, 18, 24, 24, 24, 24, 24	2	18, 18	1	24
Lost to follow up	0		1	12	0	
Depression	1	12	0		0	
Total	16		12		12	

TABLE III—*Significance of improvement (p values) in variables at 24 weeks (Wilcoxon (two tailed) test)*

	Placebo	Sulphasalazine	Sodium aurothiomalate
Erythrocyte sedimentation rate	NS	<0·005	<0·005
Haemoglobin	NS	NS	NS
Platelet count	NS	0·001	NS
Rheumatoid factor	NS	NS	0·05
Articular index	NS	<0·001	0·001
Limbering up time	NS	NS	NS
Pain score	NS	NS	<0·005
Grip strength	NS	<0·005	NS
Index of disease activity	NS	0·005	<0·005

Discussion

A second line drug in the treatment of rheumatoid arthritis is characterised by an ability to improve laboratory variables of inflammation. This study showed that sulphasalazine has a second line effect similar to that of gold, whereas placebo had no significant effect on either clinical or laboratory variables of disease activity. This is the only study published to date that has compared sulphasalazine with placebo in a double blind fashion and confirms the findings of McConkey *et al*[5 6] and Bird *et al.*[7]

The clinical value of a second line agent may be measured by the ability of patients to continue treatment with relief of symptoms in the absence of dangerous or intolerable side effects. In this study no clear differences emerged in the numbers of patients who continued to take sulphasalazine, sodium aurothiomalate, and placebo after 24 weeks. However, the reasons for dropout differed between the three groups, and of the 13 patients who stopped taking placebo because of lack of effect, eight did so before the end of the 24th week. This was despite our policy of attempting to maintain these patients on treatment for 24 weeks and contrasted appreciably with the two active regimens: only two patients taking sulphasalazine, and one taking sodium aurothiomalate stopped because of lack of effect. Toxicity in the group treated with sulphasalazine was most commonly due to nausea or vomiting, or both, six of the 30 patients stopping the drug for this reason. Symptoms affecting the upper gastrointestinal tract are believed to be dose related,[12] and the incidence of nausea and vomiting in this study may have been related to the dose used (3 g/day), which was higher than the 2 g/day dose used by McConkey *et al.*[5 6] The effects of different doses of sulphasalazine on rheumatoid arthritis have yet to be compared.

Sulphasalazine is split in the colon by bacterial action to sulphapyridine and 5-aminosalicylic acid. The former is mainly absorbed while the latter either remains largely in the bowel lumen or undergoes enterohepatic circulation. Sulphapyridine is acetylated in the liver to acetylsulphapyridine, and this is excreted more rapidly by the kidney than the unacetylated form. Slow acetylators, therefore, tend to produce higher plasma concentrations of total and free sulphapyridine than fast acetylators.[12] There was a trend in this study suggesting that gastrointestinal intolerance occurred more commonly in slow acetylators whereas lack of effect occurred in fast acetylators. This did not reach statistical significance because of small numbers, but it seems worthy of further study. Gastrointestinal intolerance may be associated with higher blood concentrations of sulphapyridine. Results in patients with inflammatory bowel disease[12 13] and in normal volunteers[14] support this theory. There is thus some promise that manipulation of the dose, perhaps with prior knowledge of acetylator state, may reduce the incidence of these side effects and allow more patients to benefit from this treatment. If such manipulation of dose proves possible sulphasalazine will have an advantage over chrysotherapy, in which monitoring of blood and tissue gold concentrations has proved unhelpful. As all the currently used second line agents are potentially toxic there is need for more, preferably safer and more easily monitored, drugs in this category.

This study shows that sulphasalazine, like intramuscular sodium aurothiomalate, produces a reduction in rheumatoid disease activity that does not occur with placebo (not even in those patients able to persevere with placebo for 24 weeks). The profile of side effects of sulphasalazine differs from that of gold in that disturbances of the upper gastrointestinal tract are more common and serious haematological and mucocutaneous problems less common. Further studies to define the appropriate dosage, possibly with prior knowledge of acetylator state, should prove worth while.

Sulphasalazine seems likely to prove a useful addition to the range of second line agents currently available for the management of patients with active rheumatoid arthritis.

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FOR THE NOSE, AND ITS INFIRMITIES—*For Polypus; or a fleshy substance growing in the Nose*—Take the juice of Ivy, and make a tent with a little cotton, the which dip in the juice and put it up in the nostril. *To cleanse the Nose*—Snuff up the juice of red Beet-root; it will cleanse not only the nose, but also the head, this is a singular remedy for such as are troubled with hard congealed stuff in their nostrils. *For bleeding at the Nose*—Bind the arms and legs as hard as you can with a piece of tape-ribboning; that, perhaps, may call back the blood. *For a Canker in the Nose*—Boil strong ale till it be thick, if the Canker be in the outside of the nose, spread it as a plaster, and apply it; if in the inside, make a tent of a linen rag, and put it up the nostril. *Another for the Polypus*—The water of Adder's-tongue snuffed up the nose, is very good: but it were better, in my opinion, to keep a rag continually moistened with it in the nose. *For bleeding at the Nose*—Take Amber and bruise into gross powder, put it upon a chafing-dish of coals, and receive the smoke up into the nose with a funnel. *Another*—When no other means will stop the bleeding at the nose, it has been known that it hath been stopped by opening a vein in the ear. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)