Co-trimoxazole in rheumatoid arthritis: a comparison with sulphapyridine

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SUMMARY The antirheumatoid activity of sulphasalazine and sulphapyridine may result from their antibacterial properties. The second line activity of sulphamethoxazole, in the form of co-trimoxazole (CTZ), has been investigated by treatment of 13 patients with RA for 24 weeks with CTZ (480 mg three times a day). The drug was found to be poorly tolerated, only five of the thirteen patients recruited completing the study. High circulating concentrations of sulphamethoxazole were found, with mean (SD) steady state serum concentrations reaching 54.02 (23.38) $\mu\text{g/ml}$. A significant reduction in serum IgM from 280 to 130 IU/l was observed, but otherwise disease activity remained unchanged or deteriorated throughout the course of the study. In contrast, patients with RA treated with sulphapyridine (1.25 g a day) showed improvement in disease activity. The results argue against an antibacterial mechanism of action for sulphasalazine and sulphapyridine in rheumatoid arthritis, unless this occurs at a site inaccessible to sulphamethoxazole.

Key word: sulphonamides.

Sulphasalazine has been shown to have specific antirheumatoid activity.^{1–6} The mechanism of action of sulphasalazine in rheumatoid arthritis (RA) is unknown, but there is evidence from two independent studies that sulphapyridine (SP), the sulphonamide component of the sulphasalazine molecule, is the active agent.^{7,8} In addition, 5-aminosalicylic acid, the salicylate moiety of sulphasalazine, does not display second line activity in RA.⁹ If SP is effective in treating RA through its antimicrobial properties it may be expected that other sulphonamides with a similar antimicrobial spectrum of activity may also have antirheumatoid properties, provided that they are accessible to the same site or sites of action as SP. Sulphamethoxazole is such a drug.

In 1972 Kalliomaki suggested that the addition of co-trimoxazole (CTZ) (1.44 g/day) to the treatment regimen of patients with RA already receiving treatment with gold, chloroquine, or steroids led to a significant reduction in erythrocyte sedimentation rate and an increase in grip strength.¹⁰ More recently, Ash *et al* have shown clinical and biochemical improvement of disease activity in a

group of 23 patients with RA treated with sulphamethoxazole (SM) (2 g/day), the sulphonamide component of CTZ.¹¹

The aim of this study was to confirm whether CTZ has second line activity in patients with RA not receiving other second line drugs, by a study protocol previously designed to evaluate possible antirheumatoid activity of various drugs.¹²

Patients and methods

Thirteen patients with classical or definite RA (American Rheumatism Association criteria), who had not received a second line drug over the preceding three months, were recruited to the study. Each patient was treated with 480 mg CTZ (Bactrim, Roche) three times a day and monitored for changes in clinical and biochemical indices of disease activity at regular intervals over a period of 24 weeks (Table 1). All clinical observations throughout the trial were carried out by the same clinical metrologist. Side effects were determined by routine haematology and biochemistry and by asking each patient at each visit to clinic the standard question: "Have the tablets upset you in any way?".

At the end of the study period, changes in disease activity for each patient were assessed by applying

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regression analysis to determine the degree of change of each parameter during treatment. A one sample, one way Student's *t* test was used to assess the significance of trends. Patients withdrawing from the trial before week 8 were excluded from statistical analysis.

Serum samples of patients completing more than eight weeks' treatment with CTZ were analysed for SM and acetylsulphamethoxazole (AcSM) concentrations by high performance liquid chromatography.¹³

The results obtained were compared with those obtained with SP (1.25 g/day) in RA using the same study protocol, with identical admission criteria.⁸ The clinical and laboratory investigators were the same in both studies. Differences in disease activity and age of patients in the two treatment groups before the onset of therapy were determined by the Mann-Whitney U test.

The dose of SP (1.25 g/day) selected is equivalent

to 2 g/day sulphasalazine, the standard maintenance dose in RA. The dose of CTZ (1.44 g/day) was chosen for two reasons: (a) the dose of SM used by Ash (2 g/day) was found to be too toxic for long term use, and Kalliomaki had demonstrated improvement in disease activity with CTZ 1.44 g/day; (b) it was comparable with the dose of SP in moles of each sulphonamide (Table 2).

Results

SIDE EFFECTS

It was originally intended to include 15 patients in the CTZ study, but owing to an overall lack of response to treatment and a high frequency of side effects, recruitment was restricted on ethical grounds to 13 patients. Only nine patients progressed beyond eight weeks' treatment with CTZ. During the course of the trial most patients developed some form of gastrointestinal disturbance or bruising, rash, itching, or mouth ulceration.

Table 1 Summary of the clinical and biochemical assessments of disease activity, recorded at each clinic visit

Parameter	Abbreviation	Method
<i>Clinical</i>		
Grip strength	GS	Sphygmomanometer cuff
Articular index	AI	Ritchie
PIP* joint circumference	JS	Arthrocircimeter
Total change score	TCS	Modified visual analogue scale
Pain score	PAIN	Daily diary card
Early morning stiffness	EMS	Daily diary card
<i>Biochemical</i>		
Full blood count	FBC	Coulter autoanalyser
Haemoglobin	Hb	Coulter autoanalyser
Erythrocyte sedimentation rate	ESR	Westergren
Plasma viscosity	PV	Capillary viscometer
Serum C reactive protein	CRP	Radial immunodiffusion
Serum immunoglobulins	Igs	Radial immunodiffusion
Serum histidine	HIST	Spectrofluorimeter
Total serum sulphhydryl	SH	Spectrophotometer
Plasma electrolytes		Vickers autoanalyser
Plasma proteins	PROT	Vickers autoanalyser
Liver function tests	LFT	Vickers autoanalyser
γ-Glutamyltranspeptidase	GGTP	Spectrophotometer

*PIP=proximal interphalangeal.

Table 2 Mean (SD) steady state serum concentrations of sulphapyridine and sulphamethoxazole and their acetyl metabolites in patients with RA

	Sulphapyridine	Sulphamethoxazole	<i>p</i> Value*
Dose (mmol/day)	5.01	4.74	
Free sulphonamide (μg/ml)	14.12 (8.19)	54.02 (23.38)	<0.001
Acetyl metabolite (μg/ml)	10.89 (6.22)	17.62 (6.76)	<0.001
Total sulphonamide (μg/ml)	25.02 (10.44)	71.63 (27.73)	<0.001

*Two sample Student's *t* test.

Table 3 Median (range) changes in disease activity during 24 weeks' treatment with co-trimoxazole (1.44 g/day) or sulphapyridine (1.25 g/day)

Parameter [‡]	Co-trimoxazole			Sulphapyridine		
	Week 0	Week 24	p Value	Week 0	Week 24	p Value
AI	21 (7-37)	26 (11-40)	<0.005*	27 (5-47)	18 (0-50)	<0.005
JS (mm)	66 (60-82)	68 (54-84)	NS	61 (54-64)	57 (52-64)	<0.025
EMS (min)	53 (0-600)	96 (0-600)	NS	115 (0-420)	4 (0-38)	NS
GS (mmHg)	96 (51-122)	86 (51-136)	NS	102 (56-148)	116 (61-200)	<0.005
PAIN	3 (1-4)	3 (2-4)	NS	3 (2-5)	2 (1-3)	<0.025
TCS	100	107 (-24-176)	NS	100	104 (96-110)	<0.010
CRP (mg/l)	<0.5 (<0.5-60.0)	6.9 (<0.5-36.6)	NS	27.5 (0.00-74.5)	<0.5 (0.00-69.0)	NS
Hb (g/l)	105 (97-124)	111 (102-133)	NS	113 (103-136)	119 (112-151)	NS
HIST (mg/l)	11.8 (8.6-13.1)	11.3 (7.5-13.4)	NS	11.5 (8.9-17.5)	16.9 (15.0-19.5)	<0.0005
PV (cP)	2.00 (1.82-2.23)	2.10 (1.90-2.41)	NS	1.95 (1.83-2.20)	1.72 (1.60-1.91)	<0.0005
SH (μmol/l)	325 (240-415)	390 (285-455)	NS	295 (175-415)	410 (235-625)	<0.025
IgM (IU/l)	280 (90-650)	130 (72-535)	<0.005	225 (50-425)	120 (45-370)	<0.005

*Denotes deterioration in disease activity.

†Table 1 lists the abbreviations.

DISEASE ACTIVITY

Changes in disease activity during treatment were determined by regression analysis¹⁴ because of the high number of patients withdrawing from the trial.

Of the patients completing a minimum of eight weeks' treatment with CTZ, the only significant improvement in disease activity was in serum immunoglobulins, IgM falling from a median of 280 IU/l at week 0 to 130 IU/l at week 24 ($p<0.005$). There was a deterioration in disease activity as judged by increases in articular index, early morning stiffness, proximal interphalangeal joint circumference, and plasma viscosity, and a fall in grip strength, but only the increase in articular index reached statistical significance (Table 3). None of the patients actually felt that CTZ had improved their condition, and no patient elected to remain on the drug at the end of the study.

There was no significant difference in the disease activity or age of patients before onset of treatment with CTZ or SP (Mann-Whitney U test). In contrast with patients treated with CTZ, there was an improvement in disease activity in patients during treatment with SP (Table 3).

STEADY STATE CONCENTRATIONS

There was a 10-fold interpatient variation in steady

state serum SM concentrations, and a threefold variation in serum AcSM concentrations. The mean steady state circulating concentration of free sulphonamides was considerably greater than that found in the group of patients treated with SP (Table 2).

There was no correlation between serum concentrations of SM or AcSM and the incidence of side effects.

Discussion

All sulphonamides are structural analogues of *p*-aminobenzoic acid, required by certain bacteria as a precursor for the synthesis of folic acid. They compete with *p*-aminobenzoic acid for the enzyme dihydropteroate synthetase and hence inhibit folic acid production. They may also become incorporated into the folate molecule in place of *p*-aminobenzoic acid, forming a 'false folate', interfering in subsequent reactions with folic acid. The *p*-amino (N_4) group of the sulphonamide molecule has to be unmasked for antimicrobial activity. Thus sulphasalazine has little antimicrobial action until SP is liberated by azo reduction within the lower gastrointestinal tract. The sulphonamides have a broad spectrum of antibacterial activity, and the

choice of sulphonamide for use in infection depends on pharmacokinetic properties rather than on differences in antibacterial activity.

It was unfortunate that side effects and ethical considerations rendered a relatively small number of patients suitable for analysis. All patients had active disease, judged by a majority of criteria, and the groups were matched for abnormality of plasma viscosity and other laboratory parameters if not for C reactive protein. Despite these reservations we still judge CTZ less effective than SP in the treatment of RA.

The results obtained with CTZ in RA were disappointing as Kalliomaki had reported success with CTZ¹⁰ and Ash *et al* with SM.¹¹ Possible reasons for this discrepancy are (a) Kalliomaki used patients already receiving second line agents or steroids, (b) the dose of SM used by Ash was 60% greater than that used in this study (2 g/day compared with 1.2 g/day).

A dose of this magnitude may be therapeutically effective in RA, but many of his patients developed hepatotoxicity, not seen with the more moderate dosage regimen used in our study. If the higher dose of SM has second line activity in RA, this suggests the risk/benefit ratio of SM in RA is very close, and will limit the use of the drug in this disease.

The antibacterial activity of the sulphonamides is dependent on the pH of the environment, the electrochemical properties of the N₁ substituted radical, and the acid dissociation constant (K_a) of the sulphonamide molecule. It has been predicted that SM (pK_a 5.7) may have greater antibacterial activity in an acidic medium, whereas SP (pK_a 8.4) may be more effective in an alkaline medium. At physiological pH the antibacterial activities of the two sulphonamides are predicted to be very similar.¹⁵

Orally administered SM is rapidly and almost totally absorbed. Ninety per cent of an administered dose can be recovered in the urine after 800 mg SM twice a day.¹⁶ The absorption of SP is slow and inconsistent,¹⁷ and only 67% of a single dose of SP (4 g orally) can be recovered in the urine.¹⁴ This may account for the considerably greater steady state serum concentrations of SM than SP after almost equimolar doses of the two sulphonamides (Table 2). If SP is effective in RA through an antimicrobial action, SM may have failed to provide benefit because it failed to reach therapeutic concentrations at the critical site of action, even though it attained greater systemic bioavailability. This site is unlikely to be the synovium as the ratio of steady state SM concentrations in synovial fluid and plasma is 1:1¹⁶ and the corresponding ratio for SP is 0.87:1.¹⁸ SM will be present in considerably greater

concentrations than SP within the synovium. Alternatively, the site of action may be within the gastrointestinal tract. This would support the hypothesis that RA may be an enteropathic arthropathy.¹⁹⁻²³ Rapid absorption of SM in the upper intestinal tract may prevent it reaching a site in the lower bowel where SP may be acting. The higher dose of SM used by Ash *et al*¹¹ may have enabled therapeutic amounts of SM to reach the more alkaline lower bowel.

Exacerbations of RA may result from microbial stimuli within the gut. The progression of the disease may then be enhanced by the release of bacterial toxins which act by activation of cell membrane phospholipase, inducing synthesis of leucotrienes, prostaglandins, and thromboxanes. Further clarification of the mechanism of action of SP in RA within the gut may come either from a trial of a 'non-absorbable' sulphonamide with a pK_a >7, or from the use of a colonic release preparation of a non-sulphonamide antibiotic with an antimicrobial spectrum similar to that of the sulphonamides.

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