Effect of acetylator phenotype on efficacy and toxicity of sulphasalazine in rheumatoid arthritis

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SUMMARY A group of 54 patients with rheumatoid arthritis (31 fast, 23 slow acetylators) treated with sulphasalazine 3 g/day were studied retrospectively. At 24 weeks no difference in the efficacy of the drug could be shown between fast and slow acetylators. In a second prospective study 40 fast acetylators were allocated to 3 g/day and 20 slow acetylators to 1.5 g/day. At 24 weeks marked improvement was seen in the fast acetylators given high dose but not the slow acetylators given low dose. It was also noted in this study that the usual ratio of fast : slow acetylators was reversed, and there is some suggestion that fast acetylators may be predisposed to more severe rheumatoid arthritis. The toxicity pattern in a total of 149 patients (83 fast, 66 slow acetylators) was also studied. Significantly more slow acetylators stopped treatment because of nausea or vomiting, or both, but serious toxicity was not confined to either group. Acetylator phenotype therefore appears important in determining the incidence of nausea and/or vomiting associated with sulphasalazine therapy in patients with rheumatoid arthritis but has no effect on the occurrence of potentially serious toxicity or efficacy. Thus prior measurement of acetylator phenotype in patients with rheumatoid arthritis confers little practical benefit in their management.

Key words: pharmacogenetics, second-line antirheumatic drugs.

Sulphasalazine has recently been resurrected as a second-line drug and has been shown to be effective in the treatment of rheumatoid arthritis.¹⁻⁵

Sulphasalazine is the azo ester of sulphapyridine and 5-aminosalicylic acid (5-ASA). Only a small proportion (about 7%) is absorbed as sulphasalazine, and the remainder reaches the large intestine, where it is split by bacterial action at its azo bond into the constituent components. The 5-ASA remains largely within the large bowel and is excreted in the faeces unchanged. Only a small amount of 5-ASA reaches the systemic circulation, and in patients with ulcerative colitis peak serum levels reach only 1-4 µg/ml (mg/l). Sulphapyridine, on the other hand, is almost totally absorbed and is eventually excreted in the urine either unchanged or after hepatic metabolism. The major hepatic metabolites are in the acetylated form, though glucuronation and hydroxylation also occur. Sul-

phapyridine is excreted in the urine more rapidly in the metabolised form.⁶ Acetylation occurs by means of hepatic (and perhaps intestinal wall) *N*-acetyltransferase. The rate of acetylation is genetically determined and follows a bimodal distribution, resulting in individuals being classed as either slow or fast acetylators. Other drugs with similar genetically determined rate of acetylation include hydralazine, procainamide, dapsone, isoniazid, other sulphonamides, phenelzine, and nitrazepam.⁷ In the United Kingdom approximately 40% of the population have been reported to be fast acetylators and 60% slow acetylators.⁸ In slow acetylators the serum half life of sulphapyridine is almost three times greater than in fast acetylators,⁹ though there is some controversy about the effect of acetylator phenotype on the steady state serum levels of sulphapyridine and its metabolites.¹⁰⁻¹³ There is good evidence, however, in both patients with ulcerative colitis and healthy volunteers that adverse effects occur more commonly in slow acetylators.^{12 14}

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In this paper we examine the effect of acetylator phenotype on the efficacy and toxicity of sulphasalazine in rheumatoid arthritis and examine whether allocation to different doses on the basis of acetylator phenotype improves the therapeutic ratio of the drug.

Patients and methods

A summary of the various patient groups studied is given in Table 1.

All patients studied suffered from classical or definite rheumatoid arthritis which remained clinically active despite optimum dosage of non-steroidal anti-inflammatory drugs (NSAIDs) and required the addition of a second-line agent in an attempt to control disease activity. As far as possible patients remained on the same NSAID at a constant dose throughout the study. No patients had known sulphonamide or salicylate sensitivity, and none had previously received sulphasalazine. Apart from two patients in study 4 (Table 1) no patients were taking or had ever taken corticosteroids for their rheumatoid arthritis, and none took other second-line drugs during the study or in the preceding three months.

All patients started on sulphasalazine (enteric coated) 0.5 g/day, and the dose was increased by weekly increments of 0.5 g/day until the allocated dose was achieved or dose related toxicity was encountered. If after 18 weeks no benefit had been achieved the dose could be increased to a maximum of 4 g/day.

The four studies described were carried out in the same centre over a three-year period. The physician treating the patients and the clinical research nurse

who carried out blind assessments were the same throughout.

Analysis of the relationship between acetylator phenotype and efficacy was carried out in two groups of patients – one retrospective (comprising the 60 patients randomly allocated to sulphasalazine 3 g/day in studies 1 and 2) and one prospective (study 3). In addition we have reviewed the effect of acetylator phenotype on toxicity of sulphasalazine in all patients shown in Table 1 in whom acetylator phenotype was available, i.e., 149 out of the total of 158.

RETROSPECTIVE STUDY GROUP

In this group acetylator phenotype was assessed retrospectively by one of the methods described in Table 2. Patients who, at the time of phenotyping were still receiving sulphasalazine had acetylator phenotype calculated from either the serum or urinary ratios of acetylated sulphapyridine : total sulphapyridine.^{16 17} Those who had discontinued sulphasalazine before phenotyping was carried out had their acetylator phenotype assessed by sulphadimidine⁸ if they were not sulphonamide sensitive and by isoniazid¹⁸ if sulphonamide sensitivity seemed likely.

Efficacy of sulphasalazine was assessed at 18 weeks, and the results of the individual studies have been reported separately.^{4 15}

PROSPECTIVE GROUP

Sixty patients (study 3 in Table 1) had acetylator phenotype assessed by an oral dose of sulphadimidine (10 mg/kg)⁸ before starting sulphasalazine. Slow acetylators were then allocated to sulphasalazine

Table 1 Summary of various studies of sulphasalazine described in this paper

Study	No of patients	Allocated dose	Method of allocation	Aim of study	Comments	No of patients with acetylator phenotype available
1 ⁴	30	3.0 g/day	Random	Comparison of efficacy of sulphasalazine with that of gold and of placebo	—	28
	30	Sodium aurothiomalate 50 mg/week			—	—
	30	Placebo 6 tabs/day				—
2 ¹⁵	30	1.5 g/day	Random	Comparison of efficacy and toxicity of two doses of sulphasalazine	—	27
	30	3.0 g/day				26
3	20	1.5 g/day	Slow acetylators	To test the hypothesis that slow acetylators require a smaller dose	—	20
	40	3.0 g/day	Fast acetylators			40
4	8	3.0 g/day	> 65 years old	To define pharmacokinetics in an elderly population	Median age 74 years (range 65–80)	8

Table 2 Various methods used to ascertain acetylator phenotype (see text)

Test drug	Dose	Sample	No of patients tested by this method (n=149)	Ratio	Fast acetylator (%)	Slow acetylator (%)	Reference
Sulphasalazine	Steady state	Plasma	44	Acetylated sulphapyridine : Acetylated sulphapyridine	>42.5	<42.5	Das and Eastwood ¹⁶
Sulphasalazine	Steady state	Urine	31	Acetylated sulphapyridine : Acetylated sulphapyridine	>65	<65	Schroder ¹⁷
Sulphadimidine	10 mg/kg	Urine	70	Acetylated sulphadimidine : Acetylated sulphadimidine	>70	<70	Price Evans ⁸
Isoniazid	10 mg/kg	Urine	4	Acetylated isoniazid	>70	<70	Schroder ¹⁷ Eidus and Hodgkin ¹⁸

zine (enteric coated) 1.5 g/day and fast acetylators to 3 g/day. The dose of 3 g/day was chosen as this is our standard clinical dose. 1.5 g/day for the slow acetylators was chosen arbitrarily, but it is the 'low dose' that we used previously in a study comparing doses.¹⁵ Assessment of efficacy was carried out at 24 weeks.

TOXICITY STUDY

Acetylator phenotype was assessed in the 149 of the total 158 patients so far treated with sulphasalazine and described in Table 1 in whom acetylator phenotype was available. These patients were followed up for 24 weeks.

STATISTICS

Appropriate non-parametric statistics were used throughout.

Results

RETROSPECTIVE GROUP

Acetylator phenotype was available in 54 of the 60 patients. Thirty-one (57%) were defined as fast acetylators and 23 (43%) as slow acetylators. By 24 weeks 19 (61%) fast and 16 (70%) slow acetylators remained on treatment. Inefficacy led to discontinuation of therapy in three of the fast acetylator group but in none from the slow acetylator group. Most patients who remained on therapy achieved their allocated dose of 3 g/day (Table 3).

Clinical and laboratory parameters of inflammation and of toxicity are shown in Table 4. At week 0 there were no significant differences between the two groups (Mann-Whitney U test, $p>0.05$). Both slow and fast acetylators showed a statistically significant improvement in most inflammatory indices, and no significant differences could be shown between slow and fast acetylators for either the 24-week values or the degree of change (Mann-Whitney U test, $p>0.05$).

PROSPECTIVE GROUP

Forty patients (66%) were fast acetylators and thus allocated to 3 g/day and 20 (33%) were slow acetylators and thus given 1.5 g/day. At 24 weeks 15 (75%) slow acetylators and 27 (68%) fast acetylators remained on treatment, again most achieved their allocated dose (Table 3). One patient in the fast acetylator group stopped because of inefficacy. Unfortunately the slow acetylator/low dose group had a significantly lower erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and higher haemoglobin (Mann-Whitney U test, $p<0.001$) at the outset of therapy. Other parameters, however, were comparable (Mann-Whitney U test, $p>0.05$). Improvement over the study period was more

readily shown in the fast acetylator/high dose group (Table 5), and the percentage fall in ESR was significantly greater in this group (Mann-Whitney U test, $p < 0.05$). Twelve high dose but only three low dose patients achieved $\geq 50\%$ improvement in ESR. Fig. 1 illustrates graphically the change in median ESR in the two. By week 24 any differences

between the groups were lost (Mann-Whitney test, $p > 0.05$).

TOXICITY DATA

Of the total 149 patients in whom acetylator phenotype was available 83 (56%) were fast and 66 (44%) were slow acetylators. Of the nine patients in

Table 3 Actual 24-week dose in various patient groups

Group	Allocated dose (g)	Actual daily dose at 24 weeks							
		0.5 g	1.0 g	1.5 g	2.0 g	2.5 g	3.0 g	3.5 g	4.0 g
Retrospective study (total)		—	1	—	4	—	30	—	—
Slow acetylators n=16	3.0	—	—	—	3	—	13	—	—
Fast acetylators n=19	3.0	—	1	—	1	—	17	—	—
Prospective study (total)		—	1	12	5	2	17	—	5
Slow acetylators/low dose n=15*	1.5	—	—	9	3	—	2	—	—
Fast acetylators/high dose n=27	3.0	—	1	3	2	2	15	—	5

*One patient temporarily off treatment at week 24.

Table 4 Medians (with ranges) for various indices at weeks 0 and 24 for patients allocated to 3 g sulphasalazine a day (retrospective study)

	Week n	Slow acetylators		Fast acetylators	
		0 23	24 16	0 31	24 19
Haemoglobin (g/l)		114 (94–142)	120 (108–150)	112 (86–170)	119** (102–177)
ESR† (mm/1st h)		71 (7–131)	25.5*** (6–77)	63.6 (18–140)	20.5***** (7–118)
Platelets $\times 10^{-9}/l$		437 (277–781)	341*** (136–448)	416 (239–888)	353***** (206–809)
Rose-Waaler titre		1/32 (0–1/1024)	1/16 (0–1/1024)	1/128 (0–1/1024)	1/64 (0–1/1024)
Ritchie articular index		20 (2–54)	7.25***** (0–33)	20 (4–61)	5.25***** (0–30)
Five point pain score		3.0 (2–4)	1.7 (0–4)	2.7 (1–4)	1.7* (1–4)
Mean hand grip strength (mmHg)		85 (46–134)	119* (9–118)	80 (40–140)	90**** (46–235)
Duration of morning stiffness (min)		66 (0–all day)	10 (0–all day)	118 (0–all day)	30* (0–all day)
IgA (g/l)		2.7 (0.4–5.1)	2.25 (1.2–3.9)	3.25 (0.7–7.5)	3.0** (0.3–5.9)
IgG (g/l)		13.4 (7.1–22.2)	12.4* (6.4–20.5)	13.25 (8.5–40.2)	11.15** (6.7–28.8)
IgM (g/l)		1.4 (0.8–3.1)	1.1* (0.7–3.4)	1.2 (0.7–7.0)	0.95* (0.4–2.1)
MCV† (fl)		81 (70–95)	90** (76–114)	82.5 (69–94)	88.5***** (74–112)
Aspartate transaminase (U/l)		15.75 (6–24)	21* (12–38)	15.5 (8–28)	16.75* (7–80)
Alanine transaminase (U/l)		8.5 (5–24)	16.25* (5–41)	14.5 (5–30)	15.75 (7–69)

* $p < 0.05$
 ** $p < 0.01$
 *** $p < 0.005$
 **** $p < 0.001$
 ***** $p < 0.0001$

†ESR=erythrocyte sedimentation rate; MCV=mean corpuscular volume.

Wilcoxon's matched pairs signed rank test, week 0 v 24.

Fig. 1 Median ESR in the slow acetylator/low dose and the fast acetylator/high dose groups.

whom acetylator phenotype was not available one had died a non-drug-related death, one had left the area, four refused to co-operate, and three had equivocal results making classification as slow or fast impossible. Toxicity rates in fast and slow acetylators were compared. Table 6 shows the reason for discontinuing therapy in the two groups over 24 weeks. Twenty-one (32%) out of 66 slow acetylators and 23 (28%) out of 83 fast acetylators ($\chi^2=0.293$, $p>0.05$) discontinued therapy before 24 weeks. In total, 18 stopped because of nausea and/or vomiting, 13 slow and five fast acetylators ($\chi^2=6.35$, $p<0.02$). No difference could be seen, however, in the overall rate of drop out because of all toxic events ($\chi^2=1.30$, $p>0.05$). In addition, Tables 4 and 5 show the results of hepatic transaminases and mean red cell volume (MCV) over the study period. Although values for these indices rose in the patients receiving 3 g/day, no differential effect of acetylator

Table 5 Medians (with ranges) for study 3 patients, i.e., fast acetylators allocated to high dose and slow acetylators allocated to low dose

	Slow acetylators/low dose		Fast acetylators/high dose		
	Week <i>n</i>	0 20	24 15	0 40	24 27
Haemoglobin (g/l)		123 (74–161)	124 (71–152)	114 (78–166)	115 (86–171)
ESR† (mm/1st h)		37.5 (2–125)	39.5 (2–115)	73 (10–150)	40**** (5–105)
Platelets ×10 ⁻⁹ /l		355 (118–607)	322 (143–502)	421 (126–802)	295**** (202–754)
Rose-Waaler titre		1/256 (0–1/1024)	1/16 (0–1/1024)	1/512 (0–1/1024)	1/128* (0–1/1024)
Ritchie articular index		17.5 (2–39)	8.5*** (0–23)	16 (0–39)	6.0**** (0–21)
Five point pain score		2.4 (1–4)	1.9 (1–4)	2.7 (1–4)	1.7**** (1–4)
Mean hand grip strength (mmHg)		67.5 (39–167)	70.5 (36–243)	83.5 (38–190)	91.5* (45–240)
Duration of morning stiffness (min)		120 (0–all day)	75 (0–all day)	76 (0–all day)	30**** (0–all day)
IgA (g/l)		3.1 (1.2–6.3)	2.3 (1.1–6.2)	3.2 (0.3–6.5)	2.7**** (0.2–5.3)
IgG (g/l)		12.3 (9.3–23.6)	10.9 (4.7–18)	14.4 (6.2–24.4)	10.4**** (4.3–20.9)
IgM (g/l)		1.1 (0.6–3.7)	1.1 (0.3–3.0)	1.4 (0.4–9.9)	1.2*** (0.2–3.3)
C-reactive protein		25.5 (6.0–40.1)	13.9 (6.0–62.1)	40.5 (6.0–100)	10.7** (6.0–42.1)
MCV (fl)		85 (71–102)	87 (69–100)	81 (66–93)	85**** (75–98)
Aspartate transaminase (U/l)		13 (6–21)	15.5 (8–301)	18 (10–39)	21* (10–104)
Alanine transaminase (U/l)		12 (4–31)	12.5 (5–282)	15 (3–40)	16 (7–42)

* $p<0.05$
** $p<0.01$
*** $p<0.005$
**** $p<0.001$ } Wilcoxon's matched pairs signed rank test, week 0 v 24.

Table 6 Reasons for and week of discontinuing therapy over first 24 weeks treatment

Reason for stopping	Slow acetylators (n=66)		Fast acetylators (n=83)	
	No stopped	Week stopped	No stopped	Week stopped
Nausea/vomiting	13 (20%)	3, 3, 3, 4, 4, 4, 6, 6, 6, 8, 12, 12, 18	5 (6%)	3, 6, 6, 12,* 20
Leucopenia	2 (3%)	6, 10	4 (5%)	1, 4, 8, 10
Rash	2 (3%)	1, 18	2 (2%)	9, 11
Mouth ulcers	0		2 (2%)	1, 2
Drowsiness	1 (1.5%)	8	0	
Dizziness	0		2 (2%)	6, 12*
Hepatitis	0		1 (1%)	18
Lack of efficacy	0		5 (6%)	18, 18, 24, 24, 24
Poor compliance	1 (1.5%)	6	0	
Intercurrent illness	1 (1.5%)	10	0	
Other	1 (1.5%)	4	3 (3.5%)	6, 6, 18
Total	21 (32%)		23 (28%)	

* Same patient.

phenotype was shown (Mann-Whitney U test, $p > 0.05$). There was no statistically significant rise, however, in the slow acetylator/low dose group.

Discussion

In this paper we aimed to assess whether acetylator phenotype affects the toxicity and efficacy of sulphasalazine in rheumatoid arthritis. It would appear that acetylator phenotype does influence the incidence of drop out because of upper gastrointestinal symptoms, with a significantly higher incidence in slow acetylators. Statistical significance was not achieved, however, when the total number of drop outs for all reasons or for all toxic events were compared. This suggests that although nausea/vomiting is related to acetylator phenotype, other toxic events are not.

This higher incidence of nausea and/or vomiting in slow acetylators is what might be expected from a study of the literature on inflammatory bowel disease and normals.^{12 14} In many instances, however, patients with rheumatoid arthritis are known to react differently from other patients to a number of drugs, and it is therefore important to confirm this relationship between slow acetylator phenotype and symptoms of nausea and/or vomiting in rheumatoid arthritis. It is also of interest to note that rheumatoid patients who were slow acetylators did not appear to show any increased toxicity with dapsone.¹⁹

The data on efficacy are unfortunately less clear cut. Probably the simplest and, to those patients concerned, the most important measure of inefficacy is the proportion of patients who failed to complete the follow-up period because of continued

severe arthritic symptoms (five (6%) fast acetylators, no slow acetylators). Such a difference between groups, however, does not achieve statistical significance, but more conclusive results might be obtained from a larger series. The retrospective data failed to show any advantages in terms of efficacy related to one particular acetylator phenotype. In the prospective study the fast acetylators/high dose patients showed improvement in more indices, and though slow acetylators/low dose patients had initially less active disease, the groups were indistinguishable in terms of disease activity at 24 weeks. This suggests that the higher dose might bring about a more favourable response even in fast acetylators and the percentage improvement in ESR was greater in this group. Overall, these findings imply that any effect of acetylator phenotype on the efficacy of sulphasalazine is minor and is far outweighed by the effect of the dose. This relationship of dose to efficacy has been previously described.¹⁵

Inclusion of retrospective data in these studies may invite criticism. However, data were only retrospective in as much as acetylator phenotype was assessed either during or after treatment, and all patients described were assessed by clinical and laboratory methods under clinical trial conditions in consecutive studies. A number of methods of assessing acetylator phenotype were used, but the literature indicates that correlation between these methods is excellent.^{16 17} Previous work has shown the sulphapyridine moiety to be the active component of sulphasalazine,²⁰ but although dose of sulphasalazine is related to efficacy, there is no relationship between serum levels of unaltered sulphapyridine and the efficacy of the drug.¹⁵ The

finding that acetylator phenotype is of little importance in determining efficacy provides further evidence for the hypothesis that a metabolite of sulphapyridine may be active or the site of action is not in equilibrium with the blood pool.

It is also noteworthy that the previously reported UK ratio of slow:fast acetylators was reversed in this study. This may suggest an ethnic difference or a difference in the rheumatoid population. Previous work in Glasgow has shown no difference in the ratio of slow:fast acetylators either in normals or in rheumatoid patients²¹ when compared with earlier English studies.⁸ Thus the reversed ratio in our case may merely be accident or may reflect a preponderance of fast acetylators among patients with rheumatoid arthritis severe enough to require second-line drugs. The latter possibility is lent some credence by the fact that in study 3 slow acetylators had milder disease.

In summary, patients with rheumatoid arthritis who are slow acetylators are more likely to stop therapy because of nausea/vomiting, but the overall drop out rate does not differ from that of fast acetylators. In addition, no statistically significant difference in efficacy could be shown between fast and slow acetylators. Thus routine assessment of acetylator phenotype before commencement of sulphasalazine does not appear to have practical value.

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