

Effects of gold, dapsone, and prednisone on serum C-reactive protein and haptoglobin and the erythrocyte sedimentation rate in rheumatoid arthritis

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SUMMARY Sequential measurements of serum C-reactive protein (CRP), serum haptoglobin (Hp), and erythrocyte sedimentation rate (ESR) were made in 209 patients with rheumatoid arthritis (RA); 78 of them were treated with gold, 71 with dapsone, and 60 with prednisone. The results were expressed as proportional changes in the measurements at 28-day intervals after treatment began. The period of study was 140 days. During treatment with gold and dapsone there were statistically significant gradual and progressive falls of similar magnitude in serum CRP and ESR. During treatment with prednisone serum CRP and ESR fell abruptly by 28 days and thereafter altered little. At 140 days prednisone had had the largest proportional effect on both measurements. During gold treatment the fall in serum Hp was similar to that of the ESR. In contrast, prednisone had little effect on Hp levels despite large falls in serum CRP and the ESR. Either prednisone stimulates Hp synthesis or the divergence is an expression of the difference in type of effect between gold and prednisone on RA. The effect of dapsone on serum Hp was large and progressive; it partly reflects haemolysis and, since the haemolysis was not progressive, partly improvement in the RA. The results show the relative efficacy of the drugs and suggest that dapsone may be a useful alternative treatment for RA.

We have discussed previously the use of sequential measurements of serum C-reactive protein (CRP) and haptoglobin (Hp) and of the erythrocyte sedimentation rate (ESR) in the management of patients with rheumatoid arthritis (RA) and the desirability of developing drugs with the capacity for lowering values of these measurements (McConkey *et al.*, 1972; McConkey *et al.*, 1973; Constable *et al.*, 1975; McConkey, 1976; Amos *et al.*, 1977). The magnitude of the effect of a drug on serum CRP, Hp, and the ESR can be regarded as a measure of its efficacy in a particular sense. The information provides a guide to how well the disease rather than just symptoms is controlled. The purpose of the present investigation was to study and compare the effects of treatment with gold, dapsone, or prednisone. We describe a method of

expressing the results which allows direct comparisons between groups of patients and provides a numerical value signifying magnitude of effect.

Patients and methods

All patients had definite or classical RA (American Rheumatism Association criteria). They were seen at 2-8-week intervals. Initial treatment was with nonsteroid anti-inflammatory drugs. If active RA persisted, as judged by clinical evidence and consistently raised serum CRP, Hp, and ESR levels, patients were then also given either gold (sodium aurothiomaleate (Myocrisin) 50 mg weekly, 78 patients), dapsone (dapsone 50 mg daily for 1 week, then 100 mg daily, 71 patients), or prednisone (prednisone 15 mg daily for 2 weeks then 10 mg daily, 60 patients). Prednisone was given to patients with more severe disease or when for some particular reason a rapid response was especially desirable.

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The majority of patients given gold were seen early in the study. Latterly we gave dapsone as an alternative, sometimes to patients who had not previously benefited from gold.

At each visit we made measurements of serum CRP (Mancini *et al.*, 1965) using a standard which gives results approximately double those obtained with commercially available standards, serum Hp as haemoglobin binding capacity (Ratcliff and Hardwicke, 1964), and the ESR (Westergren).

DATA HANDLING

Differences between the mean values of the measurements in the 3 groups at the start of treatment presented difficulties in making comparisons. Moreover, the tendency for individuals with the highest initial values to show the largest falls is not clearly evident when results are expressed as changes in the means and could bias comparisons between treatments. We therefore explored an alternative method. We first considered all patients who attended at the arbitrarily chosen time of 140 ± 14 days after gold was begun. The relationship between the initial value for serum CRP and the change from that value seemed roughly linear. Using standard least squares methods, and the fact that there were clusters of patients with the same initial values, we confirmed that the relationship for these data was adequately represented by a straight line through the origin (Bliss, 1967; Butler, 1975). The slope of the line, which is the proportional change from the initial value, could therefore be used as a measure of the effect of gold ('treatment effect') on serum CRP at 140 days. Similarly treatment effects of gold on serum Hp and the ESR at 140 days were calculated, and the method was applied to other time periods and the other drugs.

Results

The three groups of patients were roughly similar in mean age, duration of RA, the proportion with a positive Rose-Waaler (RW) test, and in their mean RW titre (Table 1). The group given prednisone

differed from the other 2 groups in having a much higher mean serum CRP.

Among the 78 patients receiving gold 34 attended at 140 ± 14 days; the relationship between initial serum CRP and the change in value at 140 days was approximately linear (Fig. 1). The slope of the line ('treatment effect') was -0.574 , signifying that in these patients values for serum CRP had fallen on average to about 43% of the starting level. The same tests and calculations were applied to other time periods for gold and for the other drugs (Table 2,

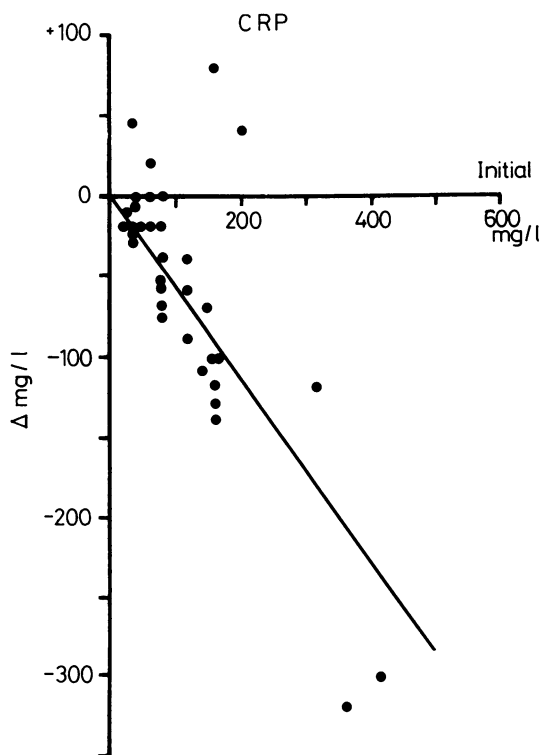


Fig. 1 Relationship between initial serum CRP and difference at 140 ± 14 days in 34 patients treated with gold.

Table 1 Particulars of the 3 groups of patients

Treatment	No. of patients (F)	Mean age years	Mean duration of RA	RW + no.	Mean RW* tube no. \pm SE	Mean CRP mg/l \pm SE	Mean Hp† mg/l \pm SE	Mean ESR mm/h \pm SE
Gold	78 (49)	46	5.2	60	3.9 ± 0.3	126.2 ± 10.8	2140 ± 80	48.1 ± 3.2
Prednisone	60 (34)	51	5.1	41	4.0 ± 0.3	165.1 ± 15.0	1990 ± 124	52.8 ± 4.8
Dapsone	71 (53)	50	6.3	51	4.3 ± 0.3	111.5 ± 10.5	1780 ± 74	51.5 ± 3.8

*Rose-Waaler titre converted to tube numbers. Tube No. 4 = 1:64. †Hp measured as mg Hb binding capacity.

Table 2 'Treatment effects'

Time : days	Treatment	Sample size	CRP		Hp		ESR	
			b†	SE (b)	b	SE (b)	b	SE (b)
28 ± 14	Gold	50	-0.244***	0.074	-0.095**	0.033	-0.099	0.051
	Prednisone	46	-0.540***	0.057	-0.192***	0.040	-0.429***	0.046
	Dapsone	64	-0.213***	0.044	-0.298***	0.048	-0.124***	0.041
56 ± 14	Gold	72	-0.168***	0.053	-0.125***	0.028	-0.123***	0.034
	Prednisone	48	-0.583***	0.056	-0.168***	0.038	-0.564***	0.043
	Dapsone	68	-0.308***	0.033	-0.400***	0.046	-0.196***	0.034
84 ± 14	Gold	46	-0.334***	0.065	-0.158***	0.035	-0.210***	0.040
	Prednisone	52	-0.606***	0.051	-0.178***	0.049	-0.512***	0.057
	Dapsone	67	-0.419***	0.035	-0.570***	0.039	-0.213***	0.036
112 ± 14	Gold	45	-0.514***	0.058	-0.302***	0.034	-0.403***	0.045
	Prednisone	40	-0.619***	0.058	-0.120	0.065	-0.457***	0.050
	Dapsone	56	-0.432***	0.145	-0.679***	0.034	-0.274***	0.042
140 ± 14	Gold	34	-0.574***	0.063	-0.275***	0.039	-0.382***	0.055
	Prednisone	34	-0.642***	0.063	-0.150*	0.064	-0.470***	0.061
	Dapsone	54	-0.465***	0.045	-0.717***	0.032	-0.296***	0.043

†The value 'b' is the slope of the line through the origin relating change from initial value to initial value.

Stars denote a slope significantly different from zero at *P<0.05, **P<0.01, ***P<0.001 probability level.

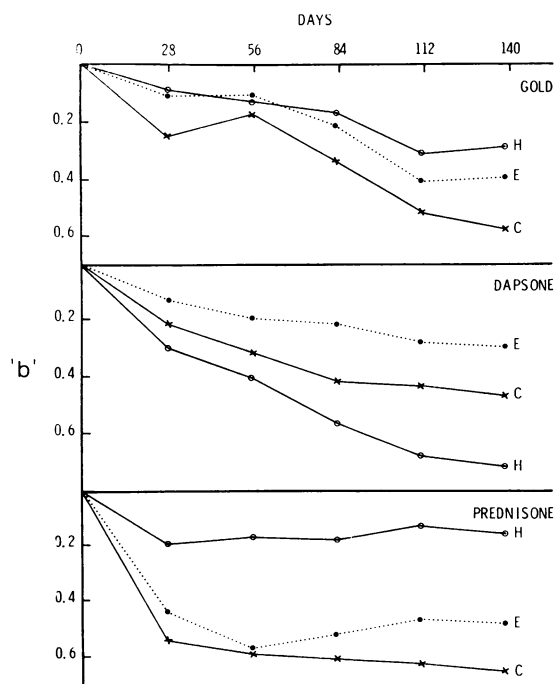


Fig. 2 Effects of gold, dapsone, and prednisone on CRP, Hp, and ESR. 'b' = the slope of the line calculated from data at each time interval.

Fig. 2). Fluctuating sample sizes were largely the consequence of irregular outpatient attendances.

During gold treatment there were statistically significant falls in serum CRP and Hp at 28 days and in ESR at 56 days; the values for each measurement continued to fall up to 140 days. During treatment

with dapsone changes in CRP and ESR were similar to those with gold, though slightly smaller; there was a large fall in serum Hp. During treatment with prednisone there were significant falls in all 3 measurements at 28 days; the falls in CRP and ESR were much larger than those resulting from gold or dapsone, but there was little further change after 56 days. The fall in Hp with prednisone at 28 days was not maintained, and by 112 and 140 days the change was smaller than at 28 days.

Discussion

By expressing the changes in the values of CRP, Hp, and ESR as the proportional fall from pretreatment levels we could make direct comparisons between the different drugs as well as between groups of patients.

In patients treated with gold an effect on CRP and Hp, and to a less extent ESR, was discernible before clinical benefit could usually be recognised. The effect was greatest on CRP, which ultimately fell at 140 days to less than half the original value, but all 3 measurements showed substantial falls and were continuing to decline at the end of the study, suggesting that there was the likelihood of further improvement.

In patients treated with dapsone the changes in CRP and ESR were similar to those with gold, though at 140 days the effects of gold were slightly greater. Gold has been shown by controlled trials (Empire Research Council, 1960; Empire Research Council, 1961) to be effective in RA. The similarity between dapsone and gold in their effects on CRP and ESR in 2 reasonably well matched groups of patients suggests that dapsone may have a place in

the treatment of this disease (McConkey *et al.*, 1976). The effect of dapsone on Hp was large, presumably owing to slight haemolysis. Such an effect is unlikely to have influenced the falls in CRP or ESR even though Hp has an augmenting effect on ESR (Fischer and Gill, 1975), because some patients had large falls in Hp but no change in CRP or ESR. Moreover, the effect cannot be solely due to haemolysis, since haemoglobin falls within days of starting treatment by about 2 g/dl and then usually remains constant, or occasionally rises.

Patients treated with prednisone had large changes in all 3 measurements at 28 days, consistent with the characteristic rapid clinical effect. However, though prednisone caused the largest falls in CRP and ESR initially, there was less difference between the 3 drugs by 140 days. The changes in CRP and ESR during prednisone treatment were roughly similar to each other; changes in Hp, however, were much smaller and by 112 days values were little different from pretreatment levels. This divergence between Hp and CRP or ESR, the latter being largely a measure of fibrinogen (Hardwicke and Squire, 1952), could be explained by assuming either that prednisone preferentially increases Hp synthesis by the liver, or that the mechanism responsible for triggering the production of acute phase proteins involves more than one mediator, and that gold and prednisone act differently. The clinical significance of this divergence is uncertain, though a drug capable of lowering all 3 measurements is likely to be better than one which affects only 2.

A number of patients stopped treatment during the study. Twenty-seven of the 78 patients given gold did so largely because of adverse effects; 11 of 71 patients stopped dapsone, usually because of inadequate effect. Thus, although the two drugs produced rather similar 'treatment effects', gold was more effective but also more toxic. Only 2 patients fell out of the prednisone group; this was because other therapy was added.

Each drug substantially lowered CRP to approximately half the initial values. Even so, mean CRP values in each group would on average have exceeded 40 mg/l, and deterioration in their RA, judged

radiographically, could still be expected though perhaps more slowly than before (Amos *et al.*, 1977).

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