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Double-blind trial of dapsone against placebo in the treatment of rheumatoid arthritis

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SUMMARY Dapsone given over 14 weeks in a dose of 50 mg a day for 1 week and thereafter 100 mg a day was found to have a beneficial effect in rheumatoid arthritis when compared with placebo administration to a matched group of patients. Significant improvement in 5 out of 7 clinical measurements and in erythrocyte sedimentation rate, viscosity, C-reactive protein was found in those patients taking dapsone. There was significant improvement compared to the placebo group in 2 out of the 7 clinical measurements and again in all 3 acute-phase reactants. The drug was quite well tolerated over the 14-week duration of the trial. The tendency to cause haemolysis will be its main limiting factor as a practical alternative to other suppressive agents currently in use.

In an open study McConkey *et al.*[1 2] suggested that dapsone possessed the properties of a suppressive agent in the treatment of rheumatoid arthritis. To investigate this further a double-blind trial was designed to compare the effects of dapsone with inert placebo in active rheumatoid arthritis.

Patients and methods

Patients selected for the study had active classical or definite rheumatoid arthritis, were aged between 18 and 65, and had had rheumatoid arthritis for less than 8 years (Table 1). Gold, penicillamine, or other suppressive agents were not administered for at least 3 months before the start of the trial. Patients on corticosteroids were admitted, but the dose of corticosteroid had to be constant for at least 6 weeks. Patients were randomly allocated dapsone or placebo and stratified for age, sex, and corticosteroid consumption. In all, 41 people entered the trial; 22 received dapsone and 19 placebo. Dapsone was administered in a dose of 50 mg a day for a week and 100 mg daily thereafter, and placebo was administered as tablets identical to dapsone tablets. The composition of the placebo was dicalcium phosphate dihydrate 94·05%, microcrystalline cellulose 4·95%, magnesium stearate 1·00%. The duration of the trial was 14 weeks and assessments were made at weeks 0, 2, 6, 10, and 14. Clinical measurements were a visual analogue scale for pain and articular index[3] for joint tenderness, grip strength by means of a sphygmodynometer and proximal interphalangeal joint (PIP) measurements by a Geigy circometer. Laboratory measurements consisted of a haemoglobin concentration, white blood cell count, platelet count, Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (by a radial immunodiffusion method), plasma viscosity, latex titre, immunoglobulin concentration (G, M, A), liver function tests, and serum haptoglobin concentrations. Antinuclear antibodies were looked for at weeks 0 and 14. Urine was checked for blood and protein at each visit by means of Multistix.

Table 1 *Details of patients*

Group	*Number*	*Sex (men)*	*Mean age (yr)*	*Disease duration*	*Steroids*
Dapsone	22	9	52·5 (27–64)	3·1	4
Placebo	19	9	50·3 (23–64)	3·5	4

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For the purposes of between-group analysis of response to treatment a mean response figure was calculated for each measurement and expressed as a percentage of the base line. The formula used was that described by Lewi and Symoens.[4] The rationale was to avoid bias due to unequal starting measurements between the 2 groups and to express response on a scale independent of the individual units of measurements. The comparison of mean responses between the 2 groups was made by Student's *t* test, and analysis of improvement within the groups was made by the paired Student's *t* test.

At each visit the patients were asked whether the treatment was suiting them.

Results

Nineteen of the 22 patients on dapsone completed the trial and 18 of the 19 on placebo.

Over the 14 weeks of the trial the patients receiving dapsone improved in all clinical measurements (Table 2) and significantly so in pain score, joint tenderness, morning stiffness, and PIP measurements. In the placebo group there was slight improvement in some measurements, but none were significant at the 5% level.

Between-group comparisons showed that, over all, the dapsone group improved more than the placebo group, but this was statistically significant in only 2 of the 7 measurements made.

All 3 measurements of acute-phase reactants showed significant improvements in the dapsone group and none in the placebo group (Table 3). There were also very significant differences between the 2 groups in mean response. There was no significant alteration in latex titres in either group, though the dapsone group tended to improve and the placebo group to deteriorate.

Clinical improvement in the dapsone group was apparent by the 10th week, though viscosity measurements showed a significant difference by week 6 (Fig. 1).

There was no significant alteration in immunoglobulin concentrations, liver function tests, and mean white cell or platelet counts. The mean haemoglobin concentration fell by 1 g/dl in the dapsone group over the 14 weeks (13·48 to 12·5 g/dl). The nadir occurred by 6 weeks, and thereafter the haemoglobin concentration began recovering. Serum haptolobin concentrations fell in all but 1 of the patients on dapsone.

Six patients in the dapsone group and 2 in the placebo group had positive antinuclear antibody (ANA) tests before the trial, and at 14 weeks 6 dapsone and 5 placebo patients had positive tests.

Four patients (3 on dapsone and 1 on placebo) failed to complete the trial (Table 4). The rash experienced was a nonthrombocytopenic purpura and resolved in a few days. The patient with nausea recovered within a few days of stopping dapsone.

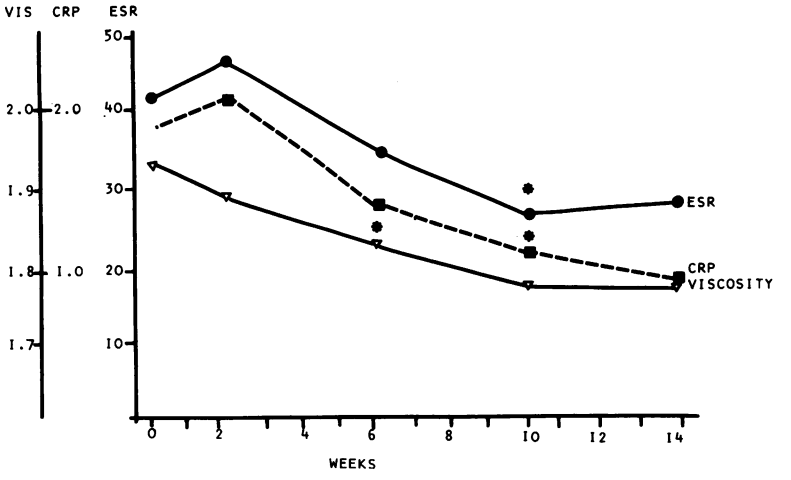
Table 2 *Clinical measurements: mean values and mean responses*

Measure	*Group*	*Week 0*	*Week 14*	*P Value week 14 cf. week 0*	*Mean response %*	*P value between mean responses*
Pain score (VAS) mm	Dapsone	45·4	26·7	<0·02	−31	NS
	Placebo	53·2	45·4	NS	−5	
Ritchie index	Dapsone	11·8	7·2	<0·01	−53	<0·025
	Placebo	14·4	13·4	NS	−13	
Morning stiffness (mins)	Dapsone	57·6	30·7	<0·05	−56	NS
	Placebo	141·4	119·9	NS	−25	
Grip R (mmHg)	Dapsone	153·3	172·6	NS	1	NS
	Placebo	147·0	142·0	NS	−13	
Grip L (mm Hg)	Dapsone	164·1	180·7	NS	0	NS
	Placebo	148·3	137·1	NS	−20	
PIP R (mm)	Dapsone	282·7	277·7	<0·05	−10	NS
	Placebo	278·4	276·9	NS	−8	
PIP L (mm)	Papsone	275·2	267·3	<0·001	−23	<0·025
	Placebo	275·3	274·1	NS	−6	

NS = not significant

Table 3 *Acute-phase reactants and latex titre: mean values and mean responses*

Measure	*Group*	*Week 0*	*Week 14*	*P value*	*Mean response %*	*P value between mean responses*
ESR (mm)	Dapsone	41·4	28·6	<0·02	−37	<0·01
	Placebo	52·2	60·6	NS	7	
CRP (mg/dl)	Dapsone	1·89	0·86	<0·01	−45	<0·01
	Placebo	3·32	4·45	NS	−2	
Viscosity (cp)	Dapsone	1·93	1·78	<0·001	−52	<0·001
	Placebo	1·97	2·04	NS	9	
Latex titre (tubes)	Dapsone	3·74	3·32	NS	−14	NS
	Placebo	3·78	4·28	NS	9	



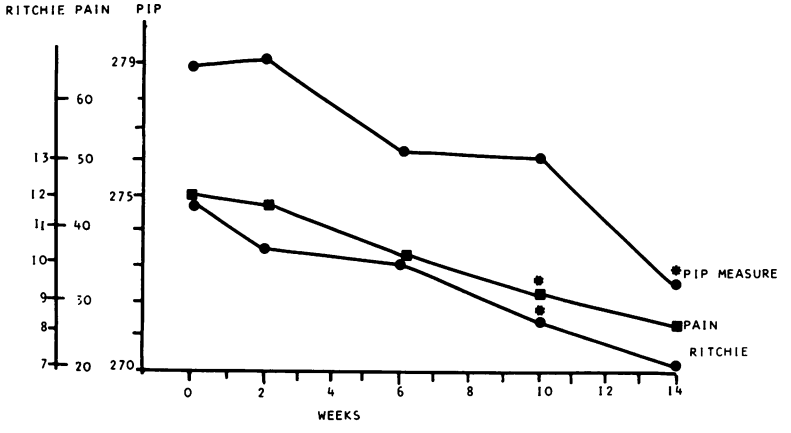


Fig. 1 *Means of acute reactants and clinical measurements against time.* *P<0·05 *cf. base line.*

Table 4 *Patients failing to complete 14 weeks*

	Reason	*Week*
Dapsone	Rash	2
	Leucopenia	2
	Nausea	6
Placebo	Deterioration in rheumatoid arthritis	10

The patient who developed an asymptomatic leucopenia by the second week was a 56-year-old woman with seropositive rheumatoid arthritis and no previous history of leucopenia. At 2 weeks the neutrophil count was $0{\cdot}8 \times 10^9$/l and by the 8th week it had risen to $2{\cdot}05 \times 10^9$/l. There was no eosinophilia, and the platelet count remained within normal limits.

An analysis of unwanted effects is shown in Tables 5 and 6 for weeks 2 and 14.

Although specifically instructed to maintain their pretrial dose of anti-inflammatory analgesics, 3

Table 5 *Affirmative replies to unwanted effect question*

	Patients completing 14 weeks	*Week 2*	*Week 14*
Dapsone	19	8	1
Placebo	18	4	3

Table 6 *Complaints classified by symptom category at weeks 2 and 14*

	Week 2		*Week 14*	
Symptom	*Dapsone*	*Placebo*	*Dapsone*	*Placebo*
Nausea, dyspepsia	6	7	1	5
Headache, muzziness	7	6	0	3
Dyspnoea, palpitations	6	4	1	2
Rash, pruritus	3	5	0	2
Total	22	22	2	12

patients in the dapsone group admitted to stopping their analgesics, and none did so in the placebo group.

Discussion

Despite randomisation and stratification the 2 groups were not as closely similar as could be hoped. The placebo group appeared to have more active disease, in particular with regard to morning stiffness and CRP measurements. Nevertheless, the results indicate that the administration of dapsone to patients with rheumatoid arthritis resulted in marked falls in the 3 acute-phase reactants measured compared to the levels in patients on inert placebo tablets.

A more modest improvement in clinical indices was seen with only 2 of the 7 measurements showing a statistically significant result at 14 weeks between the active drug and placebo. This may have been related to the duration of the trial, which was very short for a trial of this type. In Fig. 1 it can be seen that the rate of clinical improvement was continuing up to the 14th week compared to the falls in viscosity and ESR, which reached a plateau after week 10.

These results would support previous reports that dapsone exerts a suppressive effect in rheumatoid arthritis with the delayed action characteristic of this group of drugs.

As a practical exercise in assessing tolerance and toxicity the numbers of patients involved are small and the trial duration is short.

Despite the impressive list of potential unwanted effects dapsone was fairly well tolerated in the short term, although apparently less so than in McConkey's series,[1] where only 3 out of 71 patients dropped out. Dyspnoea and palpitations seemed to be related to dapsone consumption; they occurred early in the trial and were possibly caused by haemolysis. Electrocardiographic tracings failed to reveal a dysrythmia during these episodes. In the trial patients these effects were never severe enough to warrant withdrawal of the drug. Headaches would seem to be another dapsone-related side effect. The most serious unwanted effect was leucopenia, which in this case was asymptomatic and without untoward consequences, although complete recovery was prolonged. Agranulocytosis is a rare side effect of dapsone. Ognibene[5] described 16 cases of dapsone-induced agranulocytosis in otherwise apparently healthy servicemen in Vietnam who were taking dapsone as a malarial prophylactic. Half these soldiers died from agranulocyrosis. From his figures the risk of dapsone-induced agranulocytosis is about 8 per 100 000 patient exposures.

One of the most serious toxic effects is haemolysis due to an oxidant effect on red cell membranes.[6] Although no patients were glucose-6-phosphate dehydrogenase deficient, haemolysis as demonstrated by the falls in haemoglobin and profound and persistent falls in haptoglobin levels was universal, and therefore a moderate or severe anaemia would seem to be a contraindication to the use of dapsone. The lack of unwanted effects reported by patients on dapsone at the 14th week compared to the number reported by placebo patients is striking. This discrepancy may be related to the cessation or reduction of anti-inflammatory analgesic consumption in those in the dapsone group.

It is tempting to equate the action of dapsone in rheumatoid arthritis with its action in dermatitis herpetiformis, a skin disease clearly associated with an enteropathy and responding to both dapsone and a gluten-free diet. The effect of dapsone in hermatitis herpetiformis is more immediate and there is no evidence to date that gluten sensitivity is related to the pathogenesis of rheumatoid arthritis.[7 8]

The mode of action of dapsone is conjectural. Inhibition of lysosomal enzymes has been demonstrated in animal experiments,[9] although the drug's action on red cell membranes would suggest that the inhibition is not brought about by stabilising lysosomal membranes.

An immunosuppressant action has been suggested in leprosy, where a low dose is antimicrobial and a larger dose immunosuppressant and capable of modifying the borderline leprosy reaction.[10] Its antimicrobial action in leprosy is also associated with the conversion of rheumatoid-factor-positive leprosy to seronegativity.[11] A reduction in rheumatoid factor titres was not demonstrated in McConkey's series,[1] and although in this trial there was a slight reduction in rheumatoid factor titres over the 14 weeks in those patients treated with dapsone this could clearly have occurred by chance alone.

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