Antirheumatic activity of fenclofenac

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SUMMARY This study has set out to establish whether fenclofenac has an antirheumatic effect in addition to its anti-inflammatory and analgesic activity. The results show that during the course of a 6-month study the drug improved clinical parameters, including the articular index, early morning stiffness, ring sizes, and grip strength, and produced changes in laboratory measurements such as the levels of C-reactive protein, IgG, and rheumatoid factor.

A clear distinction has been made in the treatment of rheumatoid arthritis between those drugs which have anti-inflammatory/analgesic properties and a second group of drugs which have actions on the rheumatoid process itself. This latter group includes drugs such as D-penicillamine, gold, levamisole, azathioprine, and cyclophosphamide. These drugs interfere with the disease process as judged by clinical remission, a fall in erythrocyte sedimentation rate (ESR), a decline in C-reactive protein and rheumatoid factor levels, and ideally a decrease in the rate of bone erosion as judged by x-rays of the hands and feet. None of these drugs possess anti-inflammatory/analgesic properties, and they are inactive in conventional models of acute inflammation such as the rat carrageenin paw oedema. More recently alclofenac has been shown to have specific antirheumatic properties similar to the agents described above in addition to its anti-inflammatory/analgesic properties.¹ Clinically all these drugs have toxic manifestations which are on occasions lethal with the exception of alclofenac, whose main drawback is the high incidence of rashes.²

Fenclofenac is an example of an anti-inflammatory/analgesic agent with some structural similarities to alclofenac. It differs from many other nonsteroidal anti-inflammatory agents in that in animals models it is only marginally effective in the rat carrageenan paw oedema test, though it is highly effective in suppressing adjuvant arthritis in the rat.² Furthermore, the claims for its having an anti-inflammatory

activity were based on its ability to alter thermography and technetium scanning rather than on clinical grounds, where it has been shown to be an analgesic with mild anti-inflammatory activity.³ It also appears to be free of the gastrointestinal problems associated with nonsteroidal anti-inflammatory agents but which are not found with specific antirheumatic agents. For this reason it was felt important to investigate this drug to see if it possessed antirheumatic activity additional to its analgesic activity.

Patients and methods

A single-blind external observer trial was performed at King's College Hospital and Wycombe General Hospital. The trial supervisors, who were aware of the treatment allocation, were responsible for the routine management, checking of blood tests, urine analysis results, and listing unwanted side effects described by the patients. Two blind observers assessed the severity of the disease.

Outpatients attending the clinics were admitted to the trial if they were between the ages of 18 and 75 and had 'definite' or 'classical' rheumatoid arthritis (American Rheumatism Association criteria). The disease had to be severe enough for the clinician to consider the conventional use of gold or D-penicillamine.

Criteria for exclusion were: (a) Treatment in the preceding 6 months with immunosuppressives, gold, D-penicillamine, chloroquine, levamisole, systemic steroids, or alclofenac. (b) Abnormally low white blood count or platelet count at any time. (c) Evidence of intrinsic hepatic or renal dysfunction. (d)

Risk of pregnancy. (e) Patients receiving anticoagulant therapy. (f) Patients with a past history of peptic ulcer or chronic gastrointestinal symptoms unless such patients have successfully tolerated at least 2 other nonsteroidal anti-inflammatory agents during the last 12 months.

Informed consent was obtained from all patients at the beginning of the trial.

Patients were maintained on their regular doses of anti-inflammatory analgesic drugs which they had been receiving prior to the study. In addition they received either fenclofenac initially, 300 mg 3 times daily, rising where applicable to 600 mg 3 times daily, D-penicillamine, 250 mg daily with increments of 250 mg monthly or whatever was the routine practice in the unit, or placebo, 1 tablet 3 times a day, rising where indicated to 3 × 2 tablets daily. Patients were randomly allocated to any of the 3 treatments and were not otherwise stratified. Paracetamol was allowed in addition as an extra analgesic. Patients were assessed at the beginning of the trial and then at 3, 4, and 6 months during the study.

The following clinical parameters were recorded: (a) Pain on the 10 cm visual analogue scale.⁴ (b) Articular index.⁵ (c) Grip strength, (bag inflated to 30 cm, repeated 3 times, the sum of the last 2

readings of each hand being used—'Boots Bag'). (d) Ring size with the Geigy ring size measuring device. (e) Early morning stiffness measured in minutes.

Laboratory measurements were also performed, including total and differential white cell counts, platelet counts, ESR (Westergren), and the levels of C-reactive protein, IgG IgM, and rheumatoid factor (latex agglutination).

Results

The mean baseline levels for both the clinical and laboratory parameters are shown in Table 1, and no significant differences were observed between the 3 treatment groups. The changes in clinical and laboratory parameters observed after 3, 4, and 6 months of therapy with either fenclofenac or D-penicillamine and after 3 and 4 months on placebo are shown in Table 2. It was not possible to analyse the placebo group beyond 4 months owing to the large number of withdrawals within this group. No significant changes were observed within the placebo group, and, as shown in Table 3, after 6 months' treatment 13 out of 15 patients were withdrawn, 10 due to clinical ineffectiveness and 1 due to a rash.

In contrast, after 6 months' therapy with fenclofenac significant changes were observed in both clinical and laboratory parameters. Thus there were significant increases in grip strength and significant decreases in early morning stiffness, the articular

Table 1 Mean baseline clinical and laboratory parameters of patients entering trial

Treatment group	Placebo	Fenclofenac	D-penicillamine
Early morning stiffness (min)	60	70	65
Articular index	28	21	19
Ring size	575	559	574
Grip strength (mmHg)	151	183	203
Pain—visual analogue scale (mm)	55	43	50
C-reactive protein (mg 100 ml ⁻¹)	5.5	4.2	3.0
ESR (mm/h ⁻¹)	56	61	48
IgM (mg 100 ml ⁻¹)	135	170	117
IgG (mg 100 ml ⁻¹)	1450	1470	1380

Table 3 Withdrawals after 3, 4, and 6 months' therapy

	Duration of therapy in months			Total number of patients within group	Total number of withdrawals
	3	4	6		
Fenclofenac	3	2	0	16	5
D-penicillamine	2	0	2	16	4
Placebo	1	6	6	15	13

Table 2 Changes in clinical and laboratory parameters during therapy

Treatment	Placebo			Fenclofenac			D-penicillamine		
	Duration of therapy (months)			3	4	6	3	4	6
Early morning stiffness (min)	+8	−3	−25	−36*	−37*	−37*	+20	−26	−60**
Articular index	+0.5	+2.9	−3.8	−7.9	−9.2*	−9.2*	−1.6	−1.9	−0.9
Ring size	−6	−5	−6	−14**	−18**	−18**	−3	−6	−16**
Grip strength (mmHg)	−12	−6	+20	+58	+68*	+68*	+2	+23	+37
Pain—visual analogue scale (mm)	−5	0	−13	−22**	−35**	−35**	−1	−6	−14
C-reactive protein (mg 100 ml ⁻¹)	+0.4	+0.3	−0.02	−1.7*	−1.6*	−1.6*	+1.3	−0.04	−0.5
ESR (mm/h ⁻¹)	+3	+31	−8	−18**	−9	−9	−18**	−13*	−20*
IgM (mg 100 ml ⁻¹)	+11	+18	−30*	−12	−15	−15	−8	−4	+3
IgG (mg 100 ml ⁻¹)	+80	+155	−32*	−300*	−240**	−240**	+179	−62	+80

*P<0.05. **P<0.01 either by Student's *t* test or Wilcoxon matched pairs analysis.

Table 4 Side effects

Placebo		D-penicillamine		Fenclofenac	
Indigestion	2	Indigestion	7	Indigestion	3
Skin rash	2	Skin rash	3	Skin rash	1
Anaemia	1	Thrombocyto-		Transient	
		penia	1	proteinuria	1
		Constipation	1	Mouth ulcers	1
		Diarrhoea	1	Headaches	1
		Loss of taste	3		
		Headaches	1		
		Nocturia	1		

index, ring size, pain (as measured by the visual analogue scale and the levels of C-reactive protein and IgG. In addition out of 8 seropositive patients completing 6 months' therapy on fenclofenac 7 showed a decrease in rheumatoid factor titres, while 1 patient was unchanged ($P < 0.01$). Five patients receiving fenclofenac were withdrawn because of either a rash (1 patient), gastrointestinal problems (1 patient), transient proteinuria (1 patient), or clinical ineffectiveness (2 patients).

A similar clinical improvement was observed by patients undergoing therapy with D-penicillamine. After 6 months a significant improvement was observed in ring size accompanied by a significant fall in the ESR and the duration of early morning stiffness. Four patients were withdrawn, all because of clinical deterioration. Out of 8 seropositive patients 7 showed a fall in rheumatoid factor titres, while one was unchanged ($P < 0.01$). Table 4 shows the side effects in each group. The total number of side effects reported in the placebo group (5) was not significantly different from that reported in the fenclofenac group (7), while a total of 18 side effects was reported in the group receiving D-penicillamine.

Discussion

The effect of the anti-inflammatory agents is generally accepted as being different from that shown by D-penicillamine, gold, and azathioprine. This latter group of drugs are termed antirheumatic agents and produce a response only after 3 to 6 months. This response is manifested in a slow improvement in the general clinical state of the patient, which is accompanied by changes in laboratory parameters such as the ESR and the level of C-reactive protein. This particular trial was designed to ascertain whether this delayed type of response could be attributed to fenclofenac, a drug which has recently been introduced as an anti-inflammatory/analgesic drug. D-penicillamine was used as the reference drug, and in this study a placebo group was also employed to answer the question whether the results which were obtained

on the test drug could be obtained on the basis of a placebo response only.

The results here show that fenclofenac produced an improvement in clinical parameters such as the articular index and grip strength which was matched by changes in laboratory parameters such as the levels of C-reactive protein, rheumatoid factor, and IgG. The same trends were observed in the patients who received D-penicillamine, significant changes being observed in ring sizes, early morning stiffness, rheumatoid factor, and the ESR. These results suggest that fenclofenac has a long-term antirheumatic action. This cannot have arisen as the result of a placebo response, as patients on placebo showed no significant change in any clinical or laboratory parameters, and after 6 months' therapy 13 out of 15 patients were withdrawn because of either side effects or lack of clinical efficacy.

A large 'open' study has been reported by Smith,⁶ which suggests that the incidence of rashes on this drug is around 14% in the long term and that there were no other major unwanted side effects. The present study confirms these data and in addition suggests that the drug has antirheumatic activity and can be considered as an alternative treatment to the existing drugs of this group. However, these data must be confirmed by other centres, and further work will be needed to answer the question whether fenclofenac has comparable efficacy with D-penicillamine and gold on a long-term basis and also to see the true nature of the safety factor of the drug.

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References

- Berry H, Fernandes L, Ford-Hutchinson A W, Evans S J W, Hamilton E B D. Alclofenac and D-penicillamine. Comparative trial in rheumatoid arthritis. *Ann Rheum Dis* 1978; 37: 93-7.
- Atkinson D C, Leach E C. Anti-inflammatory and related properties of 2-(2, 4-dichlorophenoxy)phenylacetic acid (fenclofenac). *Agents Actions* 1976; 6: 657-66.
- Bacon P A, Davies J, Ring E F J. The use of quantitative thermography to assess the anti-inflammatory dose range of fenclofenac. *Proc R Soc Med* 1977; 70: Suppl. 6, 18-9.
- Berry H, Huskisson E C. A trial of methoprixol. *Clin Trial J* 1972; 9: 13.
- Ritchie D A, Boyle J A, McInnes J M, et al. Clinical studies with and articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968; 37: 393-406.
- Smith R B. Analysis of the side-effect patterns presenting during the course of a continuing long term open study of fenclofenac. *Proc R Soc Med* 1977; 70: Suppl. 6, 46-8.