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Alclofenac and D-penicillamine

Comparative trial in rheumatoid arthritis

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SUMMARY Forty-six patients with rheumatoid arthritis, 22 receiving D-penicillamine and 24 alclofenac, took part in a 6-month single-blind external observer trial to compare the efficacy and toxicity of these drugs in the treatment of severe rheumatoid arthritis. Both drugs were active and similar in their efficacy at 6 months as judged by clinical and laboratory measurements. Penicillamine was active therapeutically by 3 months, one month before alclofenac. 9 patients, 8 on alclofenac and one on D-penicillamine, had to stop treatment because of lack of effect or toxic effects. Skin rashes within the first week of treatment were a major problem with alclofenac and led to 6 withdrawals.

Alclofenac has been shown to have useful analgesic anti-inflammatory properties in the treatment of rheumatoid arthritis (Aylward, 1973). Further studies have suggested greater efficacy than aspirin (Aylward *et al.*, 1974) and indomethacin (Aylward *et al.*, 1975). It seemed appropriate to evaluate this drug in the management of severe rheumatoid arthritis.

D-penicillamine, originally discovered by Abraham *et al.* (1942) and first used clinically by Walshe (1956) in the treatment of Wilson's disease, has been used increasingly in the treatment of severe rheumatoid arthritis. It was first validated by the multicentre study of Andrews *et al.* (1973). Subsequently its place has been established by the finding of comparable efficacy with gold (Huskisson *et al.*, 1974) and azathioprine (Berry *et al.*, 1976). In view of the now established value of penicillamine, it was used as the comparative drug in this study.

Methods

A single-blind external observer trial was performed at King's College Hospital. The trial supervisor (H.B.), who was aware of the treatment allocation, was responsible for routine management, checking blood tests and urine analysis results, and listing unwanted side effects described by the patients. A 'blind' observer (L.F.) assessed the severity of the disease.

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PATIENT SELECTION

Outpatients attending the department of rheumatology were admitted to the trial if they were over 18 years of age and had definite or classical rheumatoid arthritis, including either positive rheumatoid factor (latex titre 1/80 or more) or erosive changes on *x*-rays of the hands, feet or both. The disease had to be severe enough for the clinician to conventionally consider the use of gold. If the patients were receiving steroid therapy, the dosage had to have been stable for the preceding 6 months. Criteria for exclusion were (a) treatment in the preceding 6 months with gold, azathioprine, or at any time with alclofenac or D-penicillamine; (b) abnormally low white cell count or platelet count at any time; (c) evidence of renal impairment (raised blood urea or serum creatinine); (d) risk of pregnancy. Informed consent was obtained from all patients at the beginning of the trial.

DRUGS

Alclofenac 1 g three times daily was compared with penicillamine 750 mg daily reached by 250 mg increments every 4 weeks. Patients were randomly allocated to either treatment and were only stratified for current corticosteroid administration. In addition to the trial drugs, patients continued to receive a

regular dose of the anti-inflammatory/analgesic drug they had been receiving before the study; this had to have been stable for the preceding month. Only paracetamol was allowed in addition. All medication was issued through normal outpatient prescribing channels.

ASSESSMENTS

The following measurements were made at the beginning of the trial and monthly for 6 months. (a) Pain using the 20-point visual analogue scale. (b) Pain using the 4-point scale (1=nil, 2=mild, 3=moderate, 4=severe. (c) Articular index (Ritchie). (d) Grip strength (bag inflated to 30 mm repeated three times, taking the sum of the last 2 readings for each hand). (e) Ring size using the Geigy ring size measuring device. (f) Early morning stiffness measured in minutes.

LABORATORY MEASUREMENTS

All laboratory measurements were made before treatment with either penicillamine or alclofenac and at monthly intervals thereafter. The erythrocyte sedimentation rate was measured by the method of Westergren. Total and differential white cell and platelet counts were performed by standard methods. IgM, IgG, and IgA were determined by fluoronephelometry using the Technicon AIP system, and IgE determined by radioimmunoassay (Pharmacia). Fibrinogen, α_1-acid glycoprotein, α_1-antitrypsin, α_2-macroglobulin, and albumin were measured by radial immunodiffusion methods (Fahey and McKelvey, 1965) using commercial reagents (Behring diagnostic reagents, Hoechst Pharmaceuticals, Hounslow, England). Urine was tested for protein and blood on each visit.

PROCEDURE

Patients were assessed monthly during the study. Treatment was stopped if the white blood cell count or platelet count fell below the lower limit of normal (white cells 4×10^9/l (4000/mm^3); platelets 150×10^9/l (150 000/mm^3)). On recovery the drug was gradually reintroduced. If the problem recurred, then the patient was withdrawn from the trial, continuation of treatment representing an unreasonable risk to the patient.

Results

Forty-six patients were admitted to the trial; 24 received alclofenac (18 female) and 22 penicillamine (16 female). 37 completed 26 weeks (16 on alclofenac and 21 on penicillamine: Table 1). 3 (2 on alclofenac and 1 on penicillamine) were withdrawn because of lack of effect and 6, all on alclofenac, were withdrawn during the first week of the trial because of skin rash. Restarting the drug produced a skin rash again. The mean age in the penicillamine group was 56·5 years and 55·9 years in the alclofenac group and the mean duration of disease was 9·4 years and 7·7 years respectively.

Table 1 *Patient selection*

	Alclofenac	*Penicillamine*
Number of patients	24 (18 females)	22 (16 females)
Mean age (years)	55·9	56·5
Mean duration of disease (years)	7·7	9·4

Table 2 *Clinical results (1) (mean values)*

	Alclofenac (A)	*Penicillamine (P)*	*Significance*		
			A v. P	*A v. initial value*	*P v. initial value*
Pain (VAS)					
Initially	10·33	9·38	NS		
3 m	10·41	6·81	,,	NS	<0·05
4 m	8·43	7·29	,,	,,	NS
5 m	9·12	7·47	,,	,,	,,
6 m	8·56	6·95	,,	,,	,,
Pain (4 point)					
Initially	2 83	2·57	NS		
3 m	2·77	2·43	,,	NS	NS
4 m	2·56	2·33	,,	,,	<0·05
5 m	2·56	2·38	,,	,,	NS
6 m	2·50	2·19	,,	,,	<0·05
Articular index					
Initially	19·3	15·5	NS		
3 m	19·8	13·3	,,	NS	NS
4 m	17·4	13·3	,,	,,	,,
5 m	21·0	13·3	,,	,,	,,
6 m	19·8	14·7	,,	,,	,,

VAS = visual analogue scale.

Table 3 *Clinical results (2) (mean values)*

	Alclofenac (A)	*Penicillamine (P)*	*Significance*		
			A v. P	*A v. initial value*	*P v. initial value*
Grip strength (mm)					
Initially	418	385	NS		
3 m	464	408	,,	NS	NS
4 m	502	433	,,	0·01	,,
5 m	495	438	,,	NS	,,
6 m	504	446	,,	<0·05	0·05
Morning stiffness (min)					
Initially	51	43	NS		
3 m	42	27	,,	NS	NS
4 m	34	29	,,	<0·05	0·05
5 m	35	25	,,	0·05	<0·05
6 m	31	21	,,	<0·01	<0·01
Ring size (mm)					
Initially	562·8	561·8	NS		
3 m	556·9	559·3	,,	NS	<0·05
4 m	557·6	558·2	,,	NS	<0·05
5 m	557·1	554·8	,,	0·01	<0·01
6 m	554·6	555·0	,,	<0·01	<0·01

The clinical and laboratory results are shown in Tables 2–5. By 3 months while there was statistically significant relief of pain (visual analogue scale), reduction in ring size, reduction in rheumatoid factor titre, ESR, fibrinogen, and IgM levels in those receiving penicillamine compared with the beginning of the trial, no such changes were seen in the patients treated with alclofenac. The improvement in haemoglobin and the fall in ESR reached significance in between-group analysis at this time. By 4 months patients treated with alclofenac showed significant improvement in grip strength, early morning stiffness, IgG and IgM levels, and improvement in haemoglobin levels compared with the beginning of the trial and comparable with the results seen with penicillamine. Figs. 1 and 2 indicate improvement in haemoglobin level and fall in ESR during the course of the trial. No significant changes were observed in the levels of α_1-acid glycoprotein, α_1-antitrypsin, albumin, α_2-macroglobulin, IgA, or IgE after treatment with either drug.

WITHDRAWALS

Eight patients were withdrawn from alclofenac therapy and one from penicillamine therapy. Skin rashes led to 6 of the alclofenac withdrawals. The other withdrawals in the trial were due to lack of effect (Table 6).

Table 4 *Laboratory results (1) (mean values)*

	Alclofenac (A)	*Penicillamine (P)*	*Significance*		
			A v. P	*A v. initial value*	*P v. initial value*
Hb (g)					
Initially	12·06	11·71			
3 m	12·08	12·69	<0·05	NS	<0·01
4 m	12·56	12·60	NS	<0·05	<0·01
5 m	12·86	12·65	,,	<0·01	<0·01
6 m	13·07	12·81	,,	<0·01	<0·01
Rheumatoid factor (dilutions)					
Initially	3·56	3·62			
3 m	3·17	2·09	NS	NS	<0·05
4 m	2·75	2·90	,,	,,	NS
5 m	3·31	2·71	,,	,,	,,
6 m	2·81	2·71	,,	,,	,,
ESR (mm)					
Initially	58·3	56·6			
3 m	52·6	39·2	0·05	NS	<0·01
4 m	39·9	34·1	NS	<0·01	<0·01
5 m	38·2	36·1	,,	<0·01	<0·01
6 m	36·1	32·0	,,	<0·01	<0·01

Table 5 *Laboratory results (2) (mean values)*

	Alclofenac (A)	*Penicillamine (P)*	*Significance*		
			A v. P	*A v. initial value*	*P v. initial value*
Fibrinogen (g/l)					
Initially	5·43	5·45			
3 m	5·18	5·09	NS	NS	<0·05
4 m	5·32	5·29	,,	,,	<0·05
5 m	5·25	4·86	,,	,,	<0·01
6 m	4·97	4·82	,,	<0·05	<0·01
IgM (g/l)					
Initially	2·89	2·06			
3 m	2·59	1·48	NS	NS	<0·01
4 m	2·46	1·52	,,	<0·05	<0·01
5 m	2·46	1·08	,,	<0·05	<0·01
6 m	2·28	1·50	,,	NS	<0·01
IgG (g/l)					
Initially	15·2	15·0			
3 m	14·5	15·9	NS	NS	NS
4 m	13·2	14·5	,,	<0·05	,,
5 m	13·1	13·0	,,	<0·01	<0·01
6 m	12·0	14·0	,,	<0·01	NS

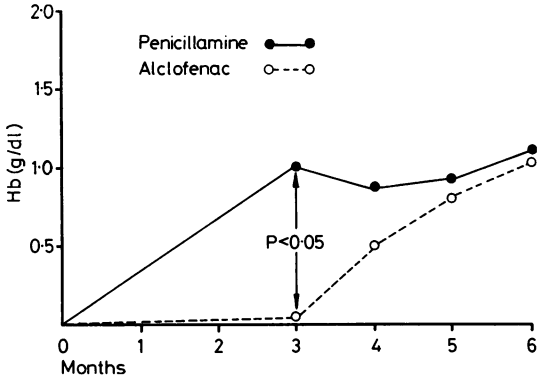

Fig. 1 *Improvement in haemoglobin concentrations.*

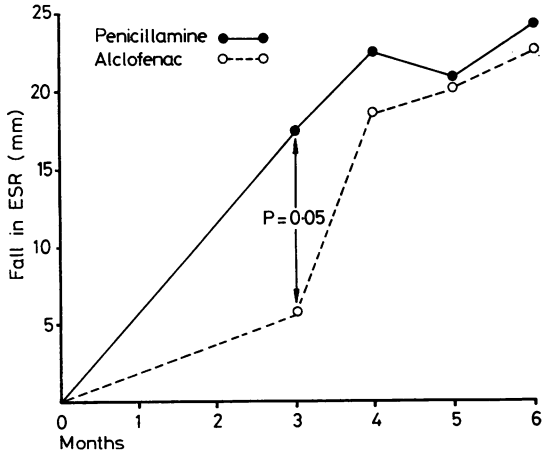

Fig. 2 *Fall in ESR.*

Table 6 *Withdrawals from trial*

	Alclofenac	*Penicillamine*
Total no.	8	1
Lack of effect (n)	2	1
Skin rash (n)	6	0

Table 7 *Unwanted side effects*

	Alclofenac	*Penicillamine*
Total no.	12	12
Taste loss	0	5
Indigestion	2	2
Nausea	0	1
Diarrhoea	0	1
Skin rash	8	0
Thrombocytopenia	0	2
Dizziness	0	1
Depression	1	0
Skin irritation	1	0

SIDE EFFECTS

Twelve side effects occurred in those patients receiving penicillamine and 12 with alclofenac. Of the penicillamine side effects, 5 were taste loss, 1 nausea, 2 indigestion, 1 diarrhoea, 1 dizziness, and 2 thrombocytopenia. 12 side effects also occurred in patients taking alclofenac. In addition to the 6 early skin rashes which led to withdrawal, there were 2 additional skin rashes that did not necessitate withdrawal because reintroduction of the drug did not reprovoke the skin rash, 1 case of skin irritation, 1 depression, and 2 indigestion (Table 7).

Discussion

It is generally accepted that there is a difference between the clinical antirheumatic effects of non-steroidal anti-inflammatory drugs, such as aspirin and indomethacin, to that induced by treatment with penicillamine, gold, and azathioprine. The latter group produce a delayed response compared with the former and their use is restricted to more severe cases of the disease due, at least in part, to their toxicity. The present trial was designed to detect the delayed type of response because any clinical improvement which was detected had to be superimposed on that produced by existing therapy. Penicillamine, which was used as the reference drug, produced the expected result. By 3 months it had caused a statistically significant improvement in pain relief, ring size, fall in ESR, fibrinogen, IgM, and rheumatoid factor, and increased haemoglobin concentration compared with the beginning of the study. The second drug, alclofenac, had been evaluated by other workers primarily with respect to its activity in comparison with aspirin and indomethacin. There was no evidence that it resembled the penicillamine-gold-azathioprine group in its effects (Aylward, 1973; Aylward *et al.*, 1974, 1975). The present results, however, showed that by 4 months patients treated with alclofenac showed significant improvement in grip strength, early morning stiffness, IgM, IgG, and haemoglobin concentrations and fall in ESR compared with the beginning of the trial.

This study confirmed the problem of skin rash related to alclofenac capsule therapy. The severe rash seemed to be an early hazard, being confined to the first week of the study. It disappeared on stopping the drug but did not recur when the patient was rechallenged. Later rashes experienced in this study were minor and on rechallenging did not recur. This was the only major problem experienced with alclofenac and is in marked contrast to the side effects seen with penicillamine which are major and potentially life-threatening hazards. These mostly occur at or beyond 9 months from the beginning of treatment and were not encountered in this 6-month study except for 2 cases of thrombocytopenia. One case has been reported of skin vasculitis which was fatal while alclofenac was being taken, but this could have been a side effect of disease rather than therapy (Billings *et al.*, 1974). So far the only long-term study of alclofenac failed to show serious toxicity (Aylward *et al.*, 1974) but more long-term work is needed before being certain that alclofenac is free of this risk. This study did not answer this question.

It must be concluded that alcofenac, as well as possessing anti-inflammatory activity similar to aspirin, also shows a penicillamine-type response and can thus be considered as an alternative treatment to gold, penicillamine, and azathioprine. Whether it should be used in this manner must depend on the results of trials conducted over a longer period, on clinical experience, and consideration of the side effects of the two drugs.

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