A biochemical comparison of alclofenac and D-penicillamine in rheumatoid arthritis

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SUMMARY In view of the claim that alclofenac has a specific antirheumatoid action a detailed biochemical study has been made over a 6-month period of 2 groups of patients with rheumatoid arthritis receiving either alclofenac or D-penicillamine for the first time. We found no biochemical evidence and little clinical evidence that alclofenac had a 'penicillamine-like' effect in rheumatoid arthritis.

Alclofenac* (4-allyloxyl-3-chlorophenylacetic acid) is a nonsteroidal anti-inflammatory agent derived from arylacetic acid. Biochemical studies have suggested, however, that this drug may have a more specific action in rheumatoid arthritis, fundamentally influencing the disease process. This evidence comes from fall in erythrocyte sedimentation rate (ESR),^{1,2} fall in immunoglobulins and latex agglutination titre but not in sheep cell agglutination test (SCAT) titre,³ rise in free plasma tryptophan,¹ and a rise in serum sulphhydryl levels.⁴

As part of a long-term study in which we are attempting to define biochemical profiles of response in patients with rheumatoid arthritis treated for the first time with 'specific' drugs we have compared the majority of these biochemical changes in patients treated either with D-penicillamine or with alclofenac. We report these results, which are at variance with those previously described.

Patients and methods

All patients had classical or definite rheumatoid arthritis (American Rheumatism Association criteria) and moderate or severe disease activity judged by the presence of at least 3 out of: (i) tenderness of 6 joints or more; (ii) swelling of more than 3 joints; (iii) morning stiffness >45 minutes; (iv) articular index⁵ >20; (v) ESR >28 mm/h.¹ Patients who had received gold, D-penicillamine, hydroxychloroquine, immunosuppressive drugs, or

alclofenac at any stage before were excluded, though patients on steady-state steroid therapy were allowed.

After a 2 week washout period on Nu-seals Aspirin 900 mg qds alone to establish clinical and biochemical baselines, patients were allocated either to alclofenac 1.0 g tds (15 patients) or D-penicillamine 125 mg/day increasing to 500 mg/day by week 8 and thereafter (15 patients). Nu-seals Aspirin, taken as required, was the only other drug allowed. Patients were seen at weeks -2, 0, 2, 4, 8, 12, 16, 20, and 24.

Eighteen biochemical and 6 immunological assessments, performed at each visit included erythrocyte sedimentation rate, plasma viscosity,⁶ C-reactive protein,⁷ total serum sulphhydryl levels,⁸ immunoglobulins, and rheumatoid factor (latex fixation and SCAT).

Clinical assessments performed at each visit were pain score (1-5 scale each night), summated change scale,⁹ duration of early morning stiffness, articular index,⁵ grip strength, joint circumference (arthrocometer), functional grade (1-5 scale), and return aspirin count.

Correlation matrices were constructed between clinical variables and the 18 biochemical variables for both D-penicillamine and alclofenac. Each biochemical variable was correlated (Pearson correlation) in turn with each clinical variable, mean figures at each of the 8 clinic visits being used.

Results

Fourteen out of 15 patients completed 24 weeks of D-penicillamine treatment, one withdrawing with a skin rash. Nine out of 15 patients completed 24

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*This drug is now discontinued.

weeks of alclofenac treatment. Reasons for withdrawal were skin rash 2, lack of effect 1, non-compliance 2, and severe diarrhoea apparently induced by alclofenac in a seropositive patient 1.

The majority of biochemical variables showed significant improvement with D-penicillamine but not with alclofenac. Fig. 1 shows changes in erythrocyte sedimentation rate, plasma viscosity,

C-reactive protein, and total serum sulphhydryl levels for the 2 drugs. Levels of significance of changes from baseline values are also shown. Of the immunological tests carried out IgM was the only parameter to change with D-penicillamine therapy, though its fall did not reach a level of statistical significance. No significant change was seen in immunoglobulins or SCAT titre in the alclofenac treated group.

Fig. 1 Serial changes in 30 patients treated either with alclofenac or D-penicillamine for (a) ESR, (b) plasma viscosity, (c) C-reactive protein, (d) total serum sulphhydryl level. Vertical lines denote standard error of the mean. Changes in individual parameters reaching statistical significance when compared with data at week 0 are indicated (Wilcoxon rank sum).

The majority of clinical variables showed improvement with D-penicillamine, not seen with alclofenac. This was most marked with articular index, which showed a significant improvement by week 16 ($P < 0.01$) and thereafter, whereas change with alclofenac did not show significant improvement. Change in summated change scale was also marked on D-penicillamine, though grip strength showed little change on either drug.

A striking difference was also observed between the 2 correlation matrices (Tables 1 and 2). Levels of significance for D-penicillamine were not only of higher order but also more frequently seen than those obtained with alclofenac.

Discussion

Although we are reluctant to draw clinical conclusions from a study in which entry was not strictly randomised, this study suggests that alclofenac did not produce the long-term clinical benefit seen with D-penicillamine. The high drop-out rate in the alclofenac treated group prevented satisfactory statistical between-group comparison towards the end of the study. Nevertheless, it appears that mean patient data for the relatively small alclofenac group remained approximately constant instead of showing the steady serial change seen with D-penicillamine.

Our study failed to confirm some of the biochemical

Table 1 Correlation matrices between clinical and biochemical variables for D-penicillamine. *P* values represent the degree of significance of correlation between mean clinical and biochemical data at each clinic visit

Systemic parameters	Clinical parameters							
	Articular index	Joint size	Summated change scale	Aspirin dose	Early morning stiffness	Grip strength	Pain score	Functional grade
Sulphydryl	0.001	0.01	0.001	0.001	0.05	0.01	0.01	0.05
Viscosity	0.001	0.001	0.001	0.01	0.01	0.05	0.01	0.05
Platelets	0.001	0.001	0.001	0.01	0.05	0.05	0.05	0.05
Bilirubin	0.001	0.01	0.01	0.001	0.05	0.01	0.05	—
CR protein	0.001	0.01	0.01	0.05	0.01	0.05	0.05	0.05
ESR	0.01	0.01	0.01	0.01	0.05	0.05	0.05	—
Albumin	0.01	0.01	0.05	0.05	0.05	0.05	—	—
Haptoglobin	0.05	0.05	0.05	0.05	0.01	0.05	—	—
GGTP	0.01	0.01	0.05	0.05	—	0.05	—	—
Haemoglobin	—	—	0.05	0.05	—	0.05	—	0.05
Alk. phos.	—	0.01	0.05	—	0.05	0.05	—	—
Fibrinogen	0.05	—	—	0.05	—	—	0.05	—
Creatinine	—	—	—	—	0.05	—	—	—
Histidine	—	—	—	—	—	0.05	—	—
Protein	0.05	0.05	—	—	—	—	—	—
WBC	—	—	—	—	—	—	0.05	—
SGOT	—	—	—	—	—	—	—	—
Globulin	—	—	—	—	—	—	—	—

Table 2 Correlation matrices between clinical and biochemical variables for alclofenac. *P* values represent the degree of significance of correlation between mean clinical and biochemical data at each clinic visit

Systemic parameters	Clinical parameters							
	Articular index	Joint size	Summated change scale	Aspirin dose	Early morning stiffness	Grip strength	Pain score	Functional grade
Sulphydryl	—	—	—	—	—	—	—	—
Viscosity	—	—	—	—	—	0.05	—	—
Platelets	—	—	0.05	—	—	—	—	—
Bilirubin	—	—	—	—	—	—	—	—
CR protein	—	—	—	—	—	—	—	—
ESR	—	—	—	—	—	—	0.05	—
Albumin	—	—	—	—	—	—	0.01	—
Haptoglobin	—	—	—	—	—	—	—	—
GGTP	—	—	—	—	—	—	—	—
Haemoglobin	—	—	0.01	0.05	—	—	—	—
Alk. phos.	0.05	—	—	—	—	—	—	—
Fibrinogen	—	—	—	—	—	—	—	—
Creatinine	—	—	—	—	—	—	—	—
Histidine	—	—	—	—	—	—	—	—
Protein	—	—	—	—	—	—	—	—
WBC	—	—	0.01	—	—	—	—	0.01
SGOT	0.05	—	—	0.05	—	—	—	—
Globulin	—	—	—	—	—	—	0.01	—

changes reported previously with alclofenac. One possible explanation is that our study differs from those previously reported, both in excluding patients who had previously received penicillamine-like drugs and in excluding concurrent medication other than aspirin.

If a drug has a fundamental action on the disease process it would be reasonable to expect simultaneous improvement in both clinical and biochemical parameters and thus a significant correlation between them. Comparison of correlation matrices for different drugs is therefore a meaningful screen on small groups of patients for possible long-term antirheumatoid activity in novel compounds. Moreover, it will not be biased by patient drop-out. It is, however, necessary to confirm that the compound under test does not make the disease significantly worse. A clear difference emerges between the correlation matrices for these 2 drugs, and our unpublished data on comparable matrices obtained from patients treated with hydroxychloroquine and gold support the validity of this comparative approach. On this basis, as well as on review of the observed clinical and biochemical changes, we have found no evidence over a 6-month period to support the view that alclofenac has a specific antirheumatoid effect. Moreover patient tolerance of this drug was poorer than for D-penicillamine.

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ADDENDUM: Alclofenac was discontinued by the manufacturers (Berk) on 29 June 1979.

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