PAPERS AND ORIGINALS

Long-term Study of Indomethacin and Alclofenac in Treatment of Rheumatoid Arthritis

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Summary

Indomethacin and alclofenac were compared for 13 months under double-blind conditions in 109 patients with active, classical, or definite rheumatoid arthritis at a relatively early stage of the disease. Both indomethacin and alclofenac were clearly effective: most patients either improved or remained as well controlled as on entry. Alclofenac proved the more effective drug, however, producing a significantly greater reduction in morning stiffness, articular index, and erythrocyte sedimentation rate, and only in the alclofenac-treated group did functional capacity improve and latex-agglutination titres diminish. Comprehensive laboratory tests showed no significant deviation from normal which could have been attributed to either drug.

Introduction

In the treatment of rheumatoid arthritis one or more non-hormonal anti-inflammatory drugs will probably be administered for several months or years, yet the few long-term controlled, double-blind assessments of such drugs show that neither non-hormonal, anti-inflammatory agents nor corticosteroids suppress inflammation sufficiently to prevent joint disease and crippling deformities (Medical Research Council and Nuffield Foundation Joint Committee, 1959, 1960). Though it seems that these drugs have little more than a brief effect on disease activity in rheumatoid arthritis they certainly provide the mainstay of current antirheumatic drug therapy, but even for this limited objective there are relatively few effective drugs and none devoid of toxicity. Duthie (1971) has argued that the modest anti-inflammatory activity possessed by current antirheumatic drugs is a factor in their favour since rheumatoid arthritis, though painful and disabling, is relatively non-lethal and functional activity can be maintained for many years (Duthie *et al.*, 1964). The various antiproliferative drugs which have produced a modest but discernible improvement in patients with rheumatoid arthritis (Mason *et al.*, 1969; Plotz, 1972; Steinburg, 1973; Currey *et al.*, 1974) have yet to be evaluated for the hazards of oncogenesis, mutagenesis, and long-term toxicity which might accompany their use in patients with relatively early disease. Reports of adverse effects on gonadal function in both sexes during the administration of antiproliferative drugs (Fairley *et al.*, 1972; Kumar *et al.*, 1972), however, raise serious doubts about their potential therapeutic efficacy in rheumatoid arthritis.

To evaluate the effects of non-steroidal antirheumatic drugs in the extended treatment of patients with rheumatoid arthritis at a relatively early stage of the disease we compared a fairly new non-steroidal antirheumatic drug, alclofenac, with an established drug, indomethacin, in a controlled, double-blind, between-patient trial over 13 months.

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Methods

Patients.—All the patients admitted to the study had "definite" or "classical" rheumatoid arthritis (American Rheumatism Association (A.R.A.) criteria) and laboratory and clinical evidence of active disease for at least one year. They were all positive for rheumatoid factor (latex test 1/80) with radiological evidence of joint erosions. Patients were excluded if they had received gold therapy, penicillamine, or antimalarial drugs during the 18 months before the trial. Patients were also excluded if they had suffered from persistent dyspepsia or were at risk of becoming pregnant. Those taking corticosteroids

were admitted only when the dose had been stable for the preceding four months.

Drugs.—Two treatments were compared: indomethacin 150–200 mg daily, and alclofenac 3–4 g daily. Each drug was given in identical capsules in divided doses of six to eight capsules a day. Patients were randomly allocated to each treatment but were stratified according to sex, duration of disease, and whether or not they were receiving corticosteroids. Initially, each patient received six capsules daily, which was increased to a maximum of eight capsules if necessary to obtain satisfactory treatment. Only paracetamol or dextropropoxyphene was allowed as a supplementary analgesic, and the consumption was recorded. Unused trial capsules and analgesic tablets were returned for counting at every visit.

Clinical Assessment.—At each visit the following assessments were made: overall joint pains (graded as severe, moderate, mild, or none); pain on palpating the joints, using the articular index of Ritchie *et al.* (1968); the duration of early morning stiffness; functional capacity (Steinbrocker *et al.*, 1949); grip strength (sphygmomanometer cuff compression); digital joint size (Boardman and Hart, 1967); and walking time over 15 metres. To assess changes in the patients' conditions during the course of the study they were grouped into 10 severity classes (A–J) at each visit according to the criteria of the American Rheumatism Association Co-operating Clinics Committee (1967). Allocation to a class was based on the patients' scores on grip strength, morning stiffness, functional capacity, and articular index.

Laboratory Investigations.—A full blood count, erythrocyte sedimentation rate (E.S.R.), blood urea, and serum enzymes (SGOT, SGPT, and lactate dehydrogenase) were recorded fortnightly for the first two months and monthly thereafter. At the same intervals standard liver function tests and urinalysis for protein, glucose, and blood were performed. Latex agglutination tests, and *x*-ray examination of hands and feet were carried out every three months.

Procedure.—After a two-week "baseline" observation period patients were assessed every four weeks. Treatment was discontinued if the patients failed to manage on the maximum daily dosage of the trial drug or developed persistent dyspepsia, proteinuria, pruritus, rash, or any other adverse effects which might have been caused by the drugs being tested.

Results

A total of 109 patients were admitted to the trial. Fifty-eight received indomethacin and 51 alclofenac. There were similar numbers of patients receiving corticosteroids in each group (eight and seven). Eighty patients completed 56 weeks of the trial, and 20 of the remaining 29 were withdrawn because of what were considered to be adverse reactions to a trial drug. Comparability of the two treatment groups on admission indicated that none of the differences were significant at the 10% (table I). The duration of disease was less than three years in 48% of all patients and less than five years in 62%.

TABLE I—*Comparability of Indomethacin-treated and Alclofenac-treated Patients with Rheumatoid Arthritis at Initial Assessment. Values are Means ± S.D.*

	Indomethacin	Alclofenac
No. of patients	58	51
Age (years)	52 ± 8·0	51 ± 9·0
Sex	29 M. 29 F.	25 M. 26 F.
Duration of disease (years)	5·2 ± 2·9	5·8 ± 2·5
Functional capacity score	2·0 ± 0·86	1·9 ± 0·83
Overall joint pain score	2·72 ± 0·75	2·74 ± 0·77
Articular index score	51·0 ± 27·3	53·6 ± 24·5
Grip strength (mm Hg)†	191 ± 21	193 ± 18
Duration of morning stiffness (min)	229 ± 5·9	231 ± 6·1
Walking time over 15 m (sec)	66 ± 49·1	73 ± 38·9
Digital joint size (mm)	499 ± 27	502 ± 25

†Grip strength values are total of values for each hand.

Double-blind conditions were adequately maintained, and the treatment was consistently guessed correctly by the clinician in only three cases (indomethacin in each case).

Both groups of patients tended to reduce their supplementary analgesic intake during the first six weeks of the trial and to increase it during the third and fourth months. During these periods there were no significant differences in analgesic requirements between the groups. From the fifth to the 13th month of the trial, however, both groups again tended to reduce their analgesic supplements, the reduction being significantly greater in the alclofenac-treated group ($P=0·025$).

CLINICAL ASSESSMENT

During the study the change in each of the seven clinical indices by which response was assessed was calculated for each patient for each month, thus allowing us to place the patients into A.R.A. severity classes A to J. We then analysed the changes in the patients' conditions which occurred during the trial.

Preliminary analysis of the data showed that those with more severe disease (initially grouped into severity classes D–G) tended to respond more favourably than those with less severe disease (classes A–C). This phenomenon might be expected since the clinical measures used allowed a greater potential for improvement in the more severely affected patients. Indeed, the initial value of a clinical index had a discernible effect on its change, and this was therefore corrected to discriminate between changes due to treatment and those dependant upon the initial severity class. The results were expressed as percentage changes and then plotted graphically against initial severity classes on the axis. Any trend dependent on initial severity scores was eliminated by weighting the percentage improvements by amounts related to the initial severity class. This weighting was achieved by varying linear multiples of the class abscissal values and testing for trend using the non-parametric Page's L-test (Page, 1963). Differences between the treatments were then analysed by using the Mann-Whitney U test.

Alclofenac produced a greater improvement than indomethacin in both the duration of morning stiffness and the articular index scores from the third month to the end of the study (table II). Improvement in functional capacity was significantly greater in the alclofenac-treated group at six months (table III), and this difference was maintained throughout the rest of the trial. No significant differences were found at any time in grip-strength, digital joint size, or walking time.

TABLE II—*Morning Stiffness and Articular Index Score at Three Months in Two Groups of Patients with Rheumatoid Arthritis*

Treatment	Morning Stiffness (min)		Articular Index	
	Mean Initial Score (± S.E.)	Mean % Reduction at 3 Months	Mean Initial Score (± S.E.)	Mean % Reduction at 3 Months
Indomethacin	224 ± 6·1	34·8	50·7 ± 3·8	12·6
Alclofenac	232 ± 5·0	68·4*	53·1 ± 3·6	30·2†

*Alclofenac was better than indomethacin $P<0·01$ (Mann-Whitney U test).
†Alclofenac was better than indomethacin $P<0·05$ (Mann-Whitney U test).

TABLE III—*Functional Capacity at Six Months and 13 Months in Two Groups of Patients with Rheumatoid Arthritis*

Treatment	Mean Initial Score (± S.E.)	Mean % Reduction of Initial Score	
		at 6 Months	at 13 Months
Indomethacin	1·9 ± 0·11	9·0	15·1
Alclofenac	1·9 ± 0·12	17·6*	49·2†

*Alclofenac better than indomethacin $P<0·05$ (Mann-Whitney U test).
†Alclofenac better than indomethacin $P<0·002$ (Mann-Whitney U test).

Classification of patients into A.R.A. severity classes on the basis of weighted percentage improvements during each three-month period of the trial indicated that the improvement noted with alclofenac was reflected in patients graduating from more severe to less severe classes. A similar phenomenon was not observed in the group receiving indomethacin.

LABORATORY INVESTIGATIONS

Erythrocyte Sedimentation Rate.—In the indomethacin-treated patients there was a median fall of 30% in the E.S.R. measurements while in 11 patients there was a mean increase of 38% (S.D. = 35%). This did not represent a statistically significant change (Wilcoxon signed ranks test: $P>0·1$). Alclofenac treatment produced a median fall of 58% in E.S.R. during 13 months—a statistically significant reduction (Wilcoxon signed ranks test: $P=0·01$).

Haematology.—Throughout the study there were no consistent changes in white cell and platelet counts in either treatment group. Haemoglobin concentration remained unchanged in patients receiving indomethacin, but after five months it had risen in the alclofenac group, and this improvement was maintained. Altogether 22·5% of

the alclofenac group as against 5·0% of the indomethacin group increased their haemoglobin concentration by 3 g/dl or more.

Rheumatoid Factor Tests.—Analysis, by a ranking procedure, of the changes in latex-agglutination titres over 13 months in each treatment group indicated that there was a statistically significant fall in titres in the alclofenac group (Wilcoxon signed ranks test; n=19; T=38; P=0·01) which did not occur in patients treated with indomethacin (n=8; T=18; P>0·10). There were no significant changes in sheep-cell agglutination titres in either group, however.

STEROID REQUIREMENTS

Steroid requirements tended to fall in both treatment groups during the first nine months of the study, but in the last three months there was a mean increase in the steroid consumption in patients receiving indomethacin. Because of the small numbers the differences between the groups were never significant (P>0·10) (table IV).

TABLE IV—*Change in Prednisolone Intake in Two Groups of Patients with Rheumatoid Arthritis. Numbers of Patients are given in Parentheses*

Treatment	Mean Initial Dose (± S.E.) (mg)	Mean Reduction in Dose (mg) at:	
		9 Months	13 Months
Alclofenac	8·2 (7)	1·6 (6)	2·3 (6)
Indomethacin	7·5 (8)	0·5 (7)	Increase of: 0·5 (7)

WITHDRAWALS

Toxicity.—There were no instances of bone-marrow suppression, apparent (biochemical) liver disturbance, raised blood urea, serious infection, or death during the 13 months. Though there were fewer withdrawals due to adverse effects among the alclofenac group than among the indomethacin group (table V) the difference was not significant. Most withdrawals were due to gastrointestinal disturbance, which had a significantly greater incidence among those receiving indomethacin.

Lack of Analgesia.—Nine patients (five on indomethacin, four on alclofenac) were withdrawn from the study because of lack of analgesia and significant increase in duration of morning stiffness. Eight were withdrawn during the first six weeks of the trial, and the remaining patient was withdrawn after four months of indomethacin treatment.

TABLE V—*Incidence of Adverse Effects leading to Withdrawal in Both Treatment Groups. Results are Numbers of Patients*

	Indomethacin	Alclofenac
Gastrointestinal disturbance	5	2
Mental confusion, nausea, and vertigo (symptom complex)	2	0
Gastric ulcer	1	0
Skin rash	1	4
Generalized pruritus	0	1
Severe sleep disturbance	2	0
Proteinuria	1	0
Severe headache	1	0
Total ..	13 (22·4%)	7 (13·7%)

Discussion

Evaluation of the effects of any drug treatment in patients with rheumatoid arthritis not only demands a controlled quantitative approach, incorporating valid measures of clinical response, but also must make allowances for the known spontaneous fluctuations in disease activity. These factors are particularly relevant to the interpretation of our data. Though ethical considerations prevented the inclusion of an "untreated" control group the clinical criteria and laboratory measures used were probably sensitive enough for assessing change in patients' conditions.

The results clearly showed the efficacy of indomethacin and alclofenac in the extended treatment of rheumatoid arthritis, though important therapeutic differences did emerge. The alclofenac group showed a significantly greater reduction in the duration of morning stiffness and in the articular index between three and 13 months, and functional capacity improved significantly only in those receiving alclofenac. Both treatment groups showed some evidence of a cortico steroid-sparing effect during the first nine months of the study, but the small numbers involved did not allow the demonstration of a statistical significance. Only in the alclofenac group was it possible to show a statistically significant reduction in E.S.R.

In 48% of patients the duration of disease activity was less than three years, and it was less than five years in 62%. If our results represent what can be achieved with relatively safe non-steroidal drugs such as indomethacin and alclofenac in the treatment of relatively early cases then the exposure of such patients to the hazards of therapy with the antiproliferative "immunosuppressive" drugs such as cyclophosphamide, azathioprine, and chlorambucil seems unjustifiable, particularly considering recent reports of their adverse effects on gonadal function (Fairley *et al.*, 1972; Kumar *et al.*, 1972).

It might be argued that our results show a spurious improvement because of the withdrawal of the most severely ill patients or the admission of those with mild disease activity and subjective improvement regardless of treatment. Analysis of the admission criteria of patients withdrawn indicated, however, that they had lesser disease activity, and rigid admission criteria ensured that the patients had active disease. Assessment of improvement based on several objective indices of response over 13 months made it most improbable that subjective improvement regardless of treatment had any effect on the results. Our results are not at variance with conclusions reached in other more comprehensive and long-term studies of patients with rheumatoid arthritis (Duthie *et al.*, 1955, 1957, 1964), which indicate that this disease is relatively benign. Most patients are satisfactorily managed with simple, safe drugs combined with measures to improve the patient's general health and wellbeing (Duthie, 1971) and relatively few patients with early disease will deteriorate much (Jacoby *et al.*, 1973).

Most patients in the trial either improved or remained as well controlled as on entry, irrespective of which drug they received. Nevertheless, alclofenac proved the more effective drug in producing clinical, haematological, and serological evidence of improvement.

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