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# Aceclofenac in Rheumatoid Arthritis: A Useful and Novel Anti-Inflammatory

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*Summary* **The efficacy and safety of 100 mg aceclofenac twice daily was investigated in 73 patients with active rheumatoid arthritis in a multi-centre, double blind, randomised, parallel group, placebo controlled study over a period of 4 weeks. Treatment with aceclofenac was effective in improving the Ritchie articular index (predetermined primary end point), duration of morning stiffness, joint swelling, ARA functional class, patient's and physician's global assessments, and pain. All these improved to a significantly ($P < 0.05$) greater extent than in placebo-treated patients. Grip strength showed a significant improvement from baseline in the aceclofenac-treated group and this was greater than the improvement measured in placebo treated patients. No significant difference was detected between the treatment groups for the number of subjects reporting an adverse event. Aceclofenac administered orally at 100 mg twice daily for four weeks thus produced significant improvements in patients with active rheumatoid arthritis. This treatment was well tolerated with an adverse event profile similar to that of placebo.**

*Key words* **Rheumatoid Arthritis, Anti-inflammatory Drug Therapy, Aceclofenac.**

## INTRODUCTION

It is regrettable that the ideal anti-inflammatory agent has yet to be developed. Corticosteroids showed great promise but their use has been restricted by adverse events (1, 2). Indomethacin has a long history of benefits to many patients but long term use is restricted by adverse events in nearly half the patients who receive it (3). More modern nonsteroidal anti-inflammatories (NSAIDs) have been developed with the emphasis on safety but no drug has fulfilled the role of an agent that might intervene in the course of inflammatory disease without significant adverse events (4, 5).

Aceclofenac is a new phenylacetic NSAID which in animals and man has been shown to be at least equivalent to diclofenac in anti-inflammatory and anti-pyretic effect.In a rodent model, gastrointestinal tolerance was better than that of indomethacin, naproxen or diclofenac and the therapeutic index of aceclofenac was four times that of diclofenac (6).

The efficacy of the drug has been demonstrated in man in single and repeat doses in studies of pain due to dental causes (7, 8) and episiotomy (9, 10) and in a number of arthritic conditions (11-15).

The purpose of this study was to confirm the previous benefits observed and compare the frequency of adverse events with patients taking placebo.

## PATIENTS AND METHODS

Patients with at least four ARA criteria for rheumatoid arthritis (16) were recruited between August 1991 and November 1992 from the out patients clinics of participating units. Ethical committee approval was obtained from the Thames Valley Independents Ethics Committee. Written informed consent was obtained from all patients prior to entry. Seventy-three of the 84 patients referred met the inclusion/exclusion criteria. The inclusion criteria were: patients of either sex aged 18-75 years, history of response to one or more NSAID in the previous year, and active disease defined by the presence of at least 3 of the following: (a) six or more tender or painful joints on motion, (b) three or more swollen joints, (c) morning stiffness of at least one hour. (d) plasma viscosity greater than or equal to 1.76 cps, or C reactive pro-

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Table I: *Demographic data*

| | Aceclofenac n = 38 | Placebo n = 35 |
|---|---|---|
| M : F | 15 : 23 | 21 : 14 |
| * Age (years) | 55.3±10.8 | 58.0± 9.9 |
| Weight (kg) | 67.0±10.8 | 72.6±15.7 |
| Height (cm) | 163.1± 8.4 | 166.6± 9.9 |

* Values are means ± SD.

tein greater than or equal to 0.7 mg/dl, or ESR greater than or equal to 20 mm/hour.

The exclusion criteria were: any of the American Rheumatism Association exclusions; arthritis before the age of 16 or of less than 3 months duration; arthritis associated with ulcerative colitis, ankylosing spondylitis, psoriasis, or inflammatory bowel disease; pregnancy; lactation; women taking inadequate contraceptive precautions; history of blood dyscrasia; recent major surgery; serious renal hepatic or cardiovascular disease; active gastro-intestinal disease; concurrent anti-coagulant therapy; diabetes treated by oral hypoglycaemic agents or inadequately stabilised on diet or insulin; concurrent ACE inhibitor therapy; previous hypersensitivity or other contraindication to nonsteroidal anti-inflammatory compounds; unexpected laboratory abnormality; treatment with intra-articular or parenteral steroids within the preceding four weeks; prior treatment with piroxicam or long-acting indomethacin within 72 hours; history of malignancy (except successfully resected basal cell carcinoma of the skin); history of alcohol or drug abuse; skin disorders precipitated or aggravated by drugs; use of gold therapy in the preceding four months or systemic corticosteroids within the preceding three months or penicillamine, anti-malarials or sulphasalazine within the preceding two months; or a history of poor compliance.

## Study design

This double-blind, randomised, placebo-controlled, parallel group study of 4 weeks duration was preceded by a washout period of up to 14 days without NSAID therapy. Randomisation was performed in blocks of 4. One tablet of either aceclofenac 100 mg or placebo was taken orally twice daily at intervals of approximately 12 hours for 4 weeks.

## Evaluation methods

Clinical assessment was performed before washout of previous NSAID, at baseline and weekly during the course of treatment. All assessments for each subject were performed by the same observer at the same time of day as far as possible. Efficacy was measured using the Ritchie articular index (17), duration of morning stiffness, grip strength, Steinbrocker grades I-III (18) and ARA functional classes I-III (16), physician's global assessment, patient's global evaluation and pain intensity on a five point scale by the physician and on a visual analog scale by the patient.

Adverse events were recorded as spontaneous complaints and solicited by an open question. In addition, vital signs were assessed at each visit and a full physical examination performed before and at the final assessment including an electrocardiogram. In seven patients taking concurrent stable anti-malarial therapy, ophthalmological assessment was also performed. Laboratory data included full blood count including differential white count, urea and electrolytes, liver function tests, urinalysis and faecal occult blood testing.

## Statistical analysis

Pre-trial and end of trial measures were compared including premature withdrawals. In addition, changes oc-

Table II: *Efficacy data: Changes in articular index, joint swelling, morning stiffness & VAS pain score.*

| | Aceclofenac (n=38) | | Placebo (n=35) | |
|---|---|---|---|---|
| | Baseline | End of treatment | Baseline | End of treatment |
| Ritchie articular | | | | |
| Index of joint tenderness+ | 20 | 12* | 24 | 17 |
| Joint swelling + | 14-30 | 7-18 | 14-32 | 10-30 |
| score | 15 | 8* | 15 | 12 |
| Morning stiffness + | 10-19 | 6-13 | 10-20 | 6-18 |
| hours | 2.4 | 1.0* | 2.5 | 2.0 |
| VAS pain + | 1.5-3.0 | 0.5-2.3 | 2.0-4.0 | 1.0-4.5 |
| (Mean ± SD) | 64.8±20.7 | 42±21.9* | 64±25.8 | 56.5±25.7 |

a Values are medians with IQ ranges except where stated.
* P<0.05: improvement over baseline measurements.
+ significant (p<0.05) advantage in aceclofenac treated group.

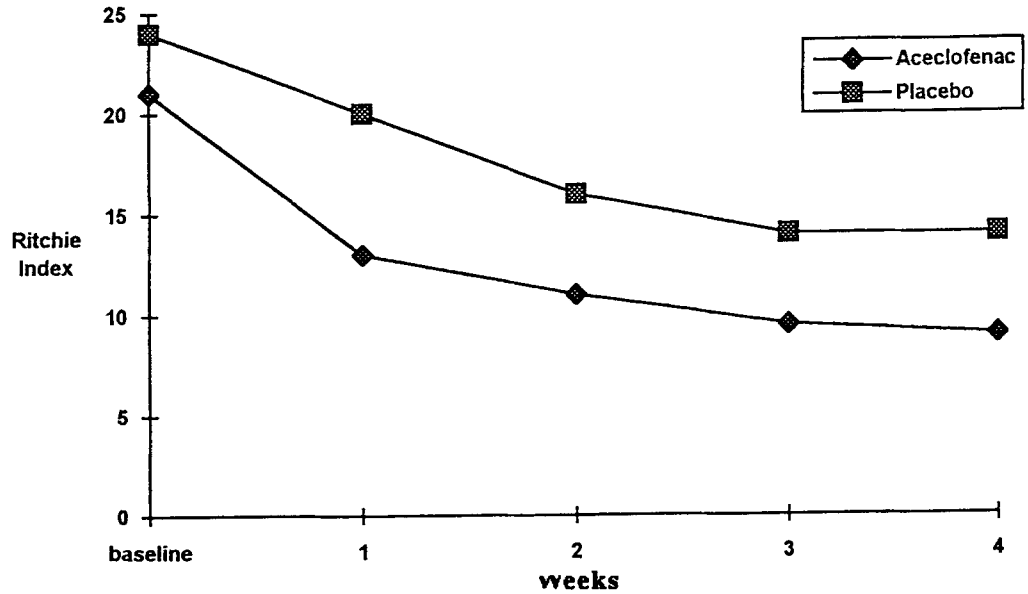


*Fig. 1:* Median changes in Ritchie Articular Index for total pain/tenderness in patients completing the study. At all time points except baseline, median values in the aceclofenac group (n=26) differed significantly ($p < 0.0001$) from those in the placebo group (n=16).

curing during treatment with aceclofenac and placebo were analysed in patients completing the treatment. The analyses were performed using the package SAS/PC version 6.04. Statistical significance was taken at a probability of less than 0.05. All statistical tests were two sided. Differences between groups were assessed using the Wilcoxon test for continuous scales and the Chi-squared test for rating scales.

The Ritchie articular index was pre-determined as the principal outcome measure. Previous studies estimated the standard deviation of articular index to be approximately 7.5. In ibuprofen-treated patients the difference in articular index from a placebo treated group was approximately 5 and on this basis, 48 subjects per treatment group would be required to detect this difference with 90% power.

## RESULTS

### Patients

Seventy-three of eighty-three patients assessed at baseline met the entry criteria. Thirty-eight received aceclofenac and thirty-five placebo. Further demographic data are shown in Table I. No significant differences were noted. There were also no differences detected in frequency of any previous medical history, concurrent illnesses or use of additional medication for unrelated illnesses.

### Efficacy

The efficacy variables are summarized in Table II. The Ritchie index of joint tenderness (Fig. 1) was similar in both treatment groups at the outset, but while the im-

Table III: *Efficacy data: changes in grip strength, ARA functional class, and physician's and patient's global assessments*

| | Aceclofenac (n = 38) | Placebo (n = 35) |
|---|---|---|
| a Change in grip strength from baseline - (mmHg) | | |
| left hand | 20* | 5 |
| | 1.7-45.3 | -6.7-12.3 |
| right hand | 31.7* | 9.3* |
| | 0-51.7 | -1.7-16.7 |
| ARA functional class+ | | |
| % Improved | 29.7 | 3 |
| % Unchanged | 70.3 | 84.9 |
| % Deteriorated | 0 | 12.1 |
| Physician's global assessment+ | | |
| % Improved | 56.8 | 30.3 |
| % Unchanged | 35.1 | 39.4 |
| % Deteriorated | 8.1 | 30.3 |
| Patient's global assessment+ | | |
| % Improved | 62.2 | 39.4 |
| % Unchanged | 29.7 | 33.3 |
| % Deteriorated | 8.1 | 27.3 |

a Values are means with IQ ranges.
* $p<0.05$: improvement over baseline measurements.
+ significant ($p<0.05$) advantage in aceclofenac treated group.

Table IV: *Adverse events.*

| | Aceclofenac No (% of subjects) | Placebo No (% of subjects) |
|---|---|---|
| Skin and appendages | | |
| Skin maculopapular rash | 1 (2.6) | |
| Musculo-skeletal | | |
| Joint stiffness | | 1(2.9) |
| Gastro-intestinal | | |
| Abdominal pain | 2 (5.3) | 1(2.9) |
| Constipation | 1 (2.6) | |
| Diarrhoea | 2. (5.3) | |
| Dyspepsia | 2 (5.3) | |
| Heartburn | 5(13.2) | 2(5.7) |
| Ingestion | | |
| Loose stools | 1 (2.6) | |
| Nausea | | 3(8.6) |
| Vomiting | | 2(5.7) |
| "Upset stomach" | 1 (2.6) | |
| Tongue pain | | 1(2.9) |
| Haemopoietic | | |
| Thrombocytopenia | | 1(2.9) |
| Renal | | |
| Raised blood creatinine/urea | 2 (5.3) | |
| Respiratory | | |
| Dyspnoea | 1 (2.6) | |
| Upper respiratory infection | 1 (2.6) | |
| General | | |
| Fever | | 1(2.9) |
| Headache | 1 (2.6) | 1(2.9) |
| Malaise | | 1(2.9) |
| Rigors | | 1(2.9) |
| Pain | | 1(2.9) |

provement in the placebo group failed to reach statistical significance (Wilcoxon test, $p=0.33$), a significant (Wilcoxon test, $p=0.0001$) advantage was demonstrated in the aceclofenac group at the end of the treatment period. The improvements from baseline were demonstrable in the aceclofenac group after one, two, three and four weeks (Wilcoxon tests, $p=0.0001$ for each interval) and at the end of the treatment the improvement in the Ritchie index was significantly greater (Wilcoxon test, $p=0.018$) in the aceclofenac than in the placebo group. Similar significant improvements were demonstrated for joint swelling with an advantage demonstrated in the aceclofenac group at end of treatment (Wilcoxon test, $p=0.038$) and improvements demonstrated over baseline values after one, two, three and four weeks (Wilcoxon tests, $p=0.0002$ at one week, $p=0.001$ at other visits).

Comparable statistically significant (Wilcoxon tests, $p \leq 0.002$) improvements in morning stiffness were also demonstrated after one (and more) week treatment with aceclofenac, but not with placebo until the final week. At the end of the treatment the improvement in the aceclofenac group was significantly greater (Wilcoxon test, $p=0.0063$) than that in the placebo group (Table II).

While improvements in grip strength (Table III) could be demonstrated at the end of the treatment period (aceclofenac group: left hand, Wilcoxon test, $p=0.0009$; Wilcoxon test, right hand $p=0.0001$), a more modest improvement was also demonstrated in the placebo-treated group in the right hand (Wilcoxon test, $p=0.035$).

Only one patient changed Steinbrocker grade through the study (data not shown) and at the end of the study there was a significant difference in ARA functional class between the treatment groups, favouring aceclofenac, (chi squared test, $p=0.047$) which was not present at baseline (Table III). The physician's and patient's global assessments showed a significant advantage of the active treatment at the end of the study (chi squared tests, $p=0.007$ and $p=0.021$).

Pain scores improved after one, two, three and four weeks in both groups but the placebo treated patients showed more modest improvements so that there was a significant advantage of aceclofenac noted after one week and at the end of treatment (chi squared tests, $p=0.014$ and $p=0.0007$) (Table II).

Based on returned tablet counts in patients completing the study, median compliance was 98.2% in the aceclofenac group and 100% in the placebo group and did not differ between groups. Paracetamol use was higher in the placebo group only after one week when a median of 6 tablets were required in the aceclofenac group as opposed to a median of 28 in the placebo group (Wilcoxon test, $p=0.015$).

**Adverse events**

Nine patients withdrew from the study prematurely in the aceclofenac group compared with 16 patients receiving placebo. Three and four patients withdrew from each group respectively because of adverse events. During the study 24 adverse events were reported by 14 patients on aceclofenac and 29 were reported by 14 patients on placebo. Table IV shows the events thought by the responsible clinicians possibly to be related to the therapy.

The patient who developed an elevated serum urea (8.6 mmol/l) and creatinine (268 umol/l) after one week on aceclofenac also developed a respiratory infection concurrently. His abnormal biochemistry resolved completely two weeks after stopping aceclofenac. Two other withdrawals due to adverse events occurred in the treatment group. One 44-year old lady developed a maculopapular rash which improved on cessation of therapy,

and a 67-year old man developed deteriorating liver function tests (before treatment he had slightly elevated alkaline phosphatase and gamma glutamyl transpeptidase but by day 25 the alanine aminotransferase had risen from 24 at baseline to 177 I.U./l and aspartate aminotransferase had risen from 22 to 88 I.U./l). These abnormalities resolved within 40 days following withdrawal from the study.

## DISCUSSION

This study confirms the benefits of aceclofenac in rheumatoid arthritis previously demonstrated in a shorter two-week study (7). All clinical features (pain, morning stiffness, swelling, tenderness & function) improved significantly when the changes were compared with patients on placebo. The frequency of side effects reported was no greater than in the placebo-treated group.

Clearly the next step is to establish data comparing aceclofenac with other NSAID's. In comparative studies with ketoprofen, it has been reported that the anti-inflammatory action is demonstrable earlier in patients treated with aceclofenac with no excess of side effects (11, 13). In another study comparing aceclofenac with ketoprofen in rheumatoid arthritis, in which aceclofenac 100 mg twice daily was compared with ketoprofen 50 mg 3 times a day for 3 months, greater improvements in the Ritchie index and morning stiffness were demonsrated within 15 days of treatment with aceclofenac (19). In this study there were more episodes leading to treatment discontinuation and adverse events in the ketoprofen-treated group.

Adverse events constitute the main problem with anti-inflammatory therapy in rheumatoid arthritis. Gastrointestinal problems are so severe in some patients that they will revert to simple analgesics as the sole symptom-relieving drug (20) whereas other patients avoid adverse events by co-prescription with an $H_2$ blocker or prostaglandin analogue (21). In a study of occult gastrointestinal bleeding (22), the increase in blood loss proved significant in volunteers taking diclofenac but no such increase was demonstrated in 6 subjects on aceclofenac 100 mg bd.

Clearly aceclofenac should be studied in much larger numbers and over more prolonged treatment periods before conclusions can be drawn, but its proven efficacy in rheumatoid arthritis and the favourable side-effects profile demonstrated in this study suggest some promise.

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