Trial of a New Antirheumatic Agent

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SUMMARY

A double-blind crossover trial of fenoprofen calcium versus acetylsalicylic acid (aspirin) and placebo in 10 outpatients with active rheumatoid arthritis, is reported.

Both fenoprofen and aspirin were found to be similarly effective agents in rheumatoid arthritis with an average daily dose of 2,1 g fenoprofen compared with 4,5 g aspirin.

No significant changes in selected laboratory tests were observed with either drug. The patients reported twice as many side-effects with aspirin; in fact, no drug-related side-effects could be attributed to fenoprofen itself. It is concluded that fenoprofen is a valuable and safe addition to the rheumatologist's armamentarium.

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The cause of and specific therapy for rheumatoid arthritis (RA) remain unknown. Antirheumatic agents are gauged to be potent when they exhibit anti-inflammatory and analgesic properties. The ideal agent should, in addition, have a wide margin of safety and a minimum of side-effects.

Fenopron (fenoprofen) is dl-2-(3-phenoxyphenyl) propionic acid, a non-steroidal compound with anti-inflammatory, antipyretic and analgesic properties in experimental animals[1] and in man.[2-4] Fenoprofen calcium is the calcium salt of the same moiety. Fenoprofen calcium and sodium share the same bio-availability, distribution and elimination in man,[5] with the calcium salt having as an advantage its lack of hygroscopic activity.

The drug is rapidly and efficiently absorbed from the gastro-intestinal tract, is tightly bound to serum albumin and has a half-life of about 160 minutes. Over 90% of the dose is metabolised, presumably by the liver; the plasma is cleared rapidly of metabolites by the kidneys. Absorption is unaffected by the administration of antacids. The mode of action, as with other antirheumatics, remains hypothetical.[6] The critical evaluation of antirheumatic agents remains fraught with difficulty. The prime aim must be to identify and measure reversible features of the disease.[7] Lee *et al.*[8] have reviewed the subject in detail and stress the need for sound experimental design based upon the selection of relevant assessment indices.

PATIENTS AND METHODS

A stage 3 double-blind crossover trial of fenoprofen versus aspirin and placebo in 10 outpatients over a 9-week period was carried out.

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Patients

Informed consent was obtained from the patients: 4 males and 6 females. The ages ranged from 26 to 69 years. All had been under the investigator's care for more than 6 months, and exhibited active rheumatoid arthritis in a steady state. Active disease is defined as exceeding the limits stated in at least 3 of the following 6 parameters: more than 6 joints painful or tender on motion; more than 3 joints swollen; more than three-quarters of an hour duration of morning stiffness; grip strength (sphygmomanometer cuff in mmHg); with male: less than 192, and female: less than 146; 15 m walking time more than 11,5 secs; and Westergren ESR more than 28 mm/hr. For the purposes of the study, steady state is defined as a 2-week period of time during which there is no change, or relatively little, occurring in the patient's clinical status.

Using criteria elaborated by the American Rheumatism Association[9] the patients were classified as probable, definite or classical RA. Furthermore 4 classes of functional capacity (class I complete function to class IV largely incapacitated, permitting little or no self-care), and 4 anatomical stages (based on radiological experiences) were used for categorising the subjects.

The outpatients' study is carried out under conditions which are much more relevant to the patients' day-to-day life. However, there is the problem of failure to take the prescribed drugs.[10] Daily and weekly tablet consumption, and count of residual drugs, were used to ascertain this.

Design of Study

The test medications were administered as identically appearing capsules of fenoprofen 200 mg and aspirin (ASA, Lilly) 500 mg, in such a way that each patient began with one week of placebo, followed by 3 weeks' therapy with either fenoprofen or aspirin, then one week placebo followed by 3 weeks' therapy with the alternate active medication, and then a final week of placebo. Each patient accrued 3 therapy weeks each for placebo, fenoprofen and aspirin, i.e. 9 weeks of observation. The actual order of medication was determined at random.

During placebo periods, patients were permitted additional aspirin 325-mg tablets *ad lib.* During the weeks of active study medication, patients were permitted additional medication in the form of propoxyphene napsylate 100-mg tablets when needed, but not exceeding 4/day.

Dosage was fixed at intervals of every 6 hours; the patients setting an alarm clock to awake for the midnight dose if necessary. The dose level was a sliding one, when active medication was taken at 1 capsule *q.i.d.* and could be increased gradually in the event of poor or inadequate

response to 3 capsules every 6 hours. The value of a variable dose lies in obviating dose-dependent negative or positive trial results.[11]

Assessment Indices

There is no single measurement which reflects the rheumatoid status. A number of criteria are therefore used in producing composite indices.[12] While all these have proved valuable in the assessment of efficacy of new compounds, none has proved superior to simple demonstration of pain relief.[13]

The following parameters were used to determine the effectiveness of medication:

Subjective evaluations were classified as follows:

1. Observer's evaluation of effect of medication since last visit (a weekly event). Scoring: very good = 1; good = 2; fair = 3; poor = 4; very poor = 5.

2. Patient's evaluation of medication since last visit. A weekly follow-up with the same scoring as 1.

3. Comfort index based on the patient's rating of his well-being regarding his arthritic pain. A daily telephonic interview, 'How do you feel today?', expressed as a weekly score: very good = 7; good = 14; fair = 21; poor = 28; very poor = 35.

4. The severity of morning stiffness ascertained every day and expressed as: none = 0; a little = 7; some = 14; a lot = 21; terrible = 28.

5. Finally the daily duration in hours of morning stiffness totalled in hours per week.

Objective evaluations were the following:

1. At the weekly follow-up, joint involvement was rated along the lines of Lansbury's articular index.[14] The number of joints involved is based upon the three features: limitation of motion, tenderness with pressure or movement and swelling. The total number of swollen joints was noted separately.

2. Grip strength. This is determined weekly by means of a sphygmomanometer cuff inflated to 20 mmHg. The average of 3 readings for each hand is expressed as the sum of the grip strengths for both hands.

3. Walking times were measured with a stop-watch as the number of seconds required for the patients to walk 15 m.

Over-all, each patient was contacted at approximately the same time each morning by telephone and questioned concerning the comfort index, morning stiffness and the number of aspirin or propoxyphene tablets taken in addition to the test medication. They were further questioned about any adverse effects experienced the previous day. General questions were placed first and were followed by leading questions about specific side-effects cited in the same order each day.[15]

At the weekly follow-up, the articular index, grip strength and walking time were recorded. The number of test tablets and/or aspirin and propoxyphene returned were counted to check patient intake. At the weekly visit, selected laboratory results to monitor safety were performed, which included full blood count, platelet counts, Westergren sedimentation rates and routine urine-analysis.

Blood-urea nitrogen (BUN), alkaline phosphatase, lactic dehydrogenase and SGOT results were recorded 5 times during the study: after first placebo week (week 1); after 3 weeks of active therapy and on the first half of the crossover (week 4); after the middle study placebo week (week 5); after 3 weeks of active medication on the last half of the crossover (week 8); and after the final placebo week. The stool was tested for occult blood twice a week.

RESULTS

The trial design provided an in-depth study of 10 patients, all of whom completed the trial. The data accumulated are copious and for the purposes of clarity and brevity 16 variables have been divided for statistical analysis into two sections—efficacy and laboratory. Table I contains the average response for each efficacy variable on the last week of active therapy and during the preceding placebo week for each regimen.

TABLE I. MEANS

Variable	Placebo week preceding fenoprofen therapy	Third week of fenoprofen therapy	Placebo week preceding aspirin therapy	Third week of aspirin therapy
Observer's evaluation	**4,0**	**2,0**	**3,8**	**2,5**
Patient's evaluation	**4,0**	**3,0**	**3,6**	**2,4**
Total No. involved joints	**36,0**	**27,1**	**34,4**	**21,6**
Number swollen joints	**14,6**	**8,9**	**12,9**	**7,6**
Grip strength	**184,5**	**246,0**	**175,5**	**263,5**
Walking time	**15,3**	**13,5**	**13,9**	**11,5**
Comfort index	**21,0**	**21,5**	**23,4**	**20,5**
Morning stiffness severity	**17,8**	**17,1**	**19,9**	**14,0**
Morning stiffness duration	**17,4**	**14,2**	**16,3**	**10,8**
ESR	**51,0**	**45,5**	**54,8**	**36,5**
Number special capsules	**59,2**	**79,3**	**65,6**	**65,8**
Ad lib. **aspirin**	**50,3**	—	**53,4**	—

TABLE II. FREQUENCIES WITH WHICH ACTIVE THERAPIES DIFFERED FROM EACH OTHER

	Ties	+	−	$P<$	Treatment concluded to be more efficacious
Observer's evaluation of condition					
Placebo-fenoprofen	1	9	0	0,01	Fenoprofen
Placebo-aspirin	1	9	0	0,05	Aspirin
Fenoprofen-aspirin	5	2	3	NS	Equal
Patient's evaluation of condition					
Placebo-fenoprofen	3	6	1	0,01	Fenoprofen
Placebo-aspirin	4	6	0	0,05	Aspirin
Fenoprofen-aspirin	6	4	0	NS	Equal
Total No. of involved joints					
Placebo-fenoprofen	0	8	2	0,10	Fenoprofen
Placebo-aspirin	0	9	1	0,05	Aspirin
Fenoprofen-aspirin	0	7	3	NS	Equal
No. of swollen joints					
Placebo-fenoprofen	1	9	0	0,01	Fenoprofen
Placebo-aspirin	1	8	1	0,05	Aspirin
Fenoprofen-aspirin	2	4	4	NS	Equal
Grip strength					
Placebo-fenoprofen	0	1	9	0,05	Fenoprofen
Placebo-aspirin	0	2	8	0,10	Aspirin
Fenoprofen-aspirin	0	5	5	NS	Neither
Walking time					
Placebo-fenoprofen	0	9	1	0,05	Fenoprofen
Placebo-aspirin	0	7	3	NS	Neither
Fenoprofen-aspirin	0	5	5	NS	Neither
Weekly total comfort index					
Placebo-fenoprofen	2	4	4	NS	Neither
Placebo-aspirin	0	7	3	NS	Neither
Fenoprofen-aspirin	1	5	4	NS	Neither
Morning stiffness severity (weekly total)					
Placebo-fenoprofen	1	4	5	NS	Neither
Placebo-aspirin	2	6	2	NS	Neither
Fenoprofen-aspirin	0	6	4	NS	Neither
Morning stiffness duration (weekly total)					
Placebo-fenoprofen	0	5	5	NS	Neither
Placebo-aspirin	1	6	3	NS	Neither
Fenoprofen-aspirin	1	6	3	NS	Neither
ESR					
Placebo-fenoprofen	4	4	2	NS	Neither
Placebo-aspirin	0	9	1	0,05	Aspirin
Fenoprofen-aspirin	0	6	4	NS	Neither
Weekly total—No. special capsules taken					
Placebo-fenoprofen	1	0	9	0,01	
Placebo-aspirin	0	6	4	NS	
Fenoprofen-aspirin	0	8	2	NS	

TABLE III. MEANS

Variable	Normal	Placebo week preceding fenoprofen therapy	Third week of fenoprofen therapy	Placebo week preceding aspirin therapy	Third week of aspirin therapy
BUN	7-20 mg/100 ml	15,5	18,7	15,3	21,4
Alkaline phosphatase	9-35 IU	29,3	28,0	28,9	27,3
LDH	40-100	142,1	136,1	132,4	130,4
SGOT	<28	20,7	19,5	16,8	23,8

Table II presents the frequencies with which the active therapies differed from each other and their corresponding preceding placebo weeks. In this Table, a $P = 0,10$ cutoff has been used rather than the more conventional 0,05 because of the small number of subjects. A simple binomial test was applied pairwise to discriminate among the treatments. Comparisons with placebo are single-tailed tests; those between fenoprofen and aspirin are two-tailed. The conclusions which were made as a result of these tests are presented in this table.

Tables III and IV are the laboratory analogues to Tables I and II. They are identical with the efficacy tables, with the exception that all tests have two-sided alternatives.

Efficacy Factors

Examination of Tables I and II indicates the similarity between fenoprofen and aspirin at the doses used in this study. In fact, no differences were observed between fenoprofen and aspirin which could not be readily assigned to random variation. Both fenoprofen and aspirin were superior to placebo for most of the efficacy parameters.

The number of *ad lib.* aspirin taken during the preceding placebo week was comparable for the fenoprofen and aspirin regimens. Propoxyphene consumption was irregular and does not indicate a substantial difference between the regimens.

TABLE IV. FREQUENCIES WITH WHICH ACTIVE THERAPIES DIFFERED FROM EACH OTHER IN LABORATORY VALUES

	Ties	+	−	*P*
BUN				
Placebo-fenoprofen	0	1	9	0,05
Placebo-aspirin	0	3	7	NS
Fenoprofen-aspirin	0	4	6	NS
Alkaline phosphatase				
Placebo-fenoprofen	1	6	3	NS
Placebo-aspirin	0	7	3	NS
Fenoprofen-aspirin	0	6	4	NS
LDH				
Placebo-fenoprofen	0	5	5	NS
Placebo-aspirin	0	5	5	NS
Fenoprofen-aspirin	0	5	5	NS
SGOT				
Placebo-fenoprofen	2	2	6	NS
Placebo-aspirin	1	2	7	NS
Fenoprofen-aspirin	1	4	5	NS

Laboratory Values

Laboratory values were essentially the same during placebo, aspirin and fenoprofen periods, with one exception. There was an apparent increase in blood-urea nitrogen during the active therapy periods as compared with

TABLE V. FINAL EVALUATION: COMPARISON OF ASPIRIN AND FENOPROFEN (FPN)

Efficacy	Side-effects	Comparison with previous therapy	Medication dose acceptability
Aspirin better	**None**	**Patients better during both periods of study than with steroids**	**Both well tolerated**
FPN better	**None**	**Better with FPN than when on indomethacin**	**Both well tolerated**
FPN better	**None**	**Better during both periods as compared with previous indomethacin**	**Both well tolerated**
Equal	**Present with aspirin only**	**Both study periods were better than any previous therapy**	**FPN better tolerated**
Equal	**None**	**Both study periods better than previous phenylbutazone therapy**	**Both well tolerated**
Equal	**Present with aspirin only**	**Both study periods rated equal to phenylbutazone**	**Both well tolerated**
Equal	**Present with aspirin only**	**Both study periods rated equal to phenylbutazone and indomethacin**	**FPN better tolerated**
FPN better	**None**	**FPN better than any previous therapy**	**Both well tolerated**
FPN better	**Present with aspirin only**	**FPN better than indomethacin and aspirin**	**FPN better tolerated**
Aspirin better	**Present with aspirin only**	**Both study periods better than indomethacin**	**FPN better tolerated**

Comments on the final summary form were based solely upon objective evaluation of each patient since this was a double-blind study. The drug code has been added to these comments summarised in this Table to facilitate the comparison.

placebo, fenoprofen and aspirin being similar in this respect.

In conclusion, fenoprofen and aspirin were similarly effective in ameliorating the symptoms of rheumatoid arthritis and were associated with similar effects on observed laboratory values.

Assessment

Table V is a compilation of the investigator's comments on the patients' final summary forms. The objective assessment of each patient's progress has been tabulated. For efficacy, aspirin was rated the better therapy in 2 patients, fenoprofen the better therapy in 4 patients, and 4 patients were rated as having equally effective therapy. As to side-effects, 5 patients were rated as having side-effects with aspirin only and no patients were reported to have side-effects with fenoprofen.

In the comparison of study medications with previous therapy, all 10 patients were rated as better on the trial than with previous therapy, which included corticosteroids, indomethacin and phenylbutazone. Seven patients were rated as better during both drug periods, and 3 patients were better during fenoprofen therapy than on previous medication. These ratings to a great extent represent the patient input to the physician. One was impressed by the positive effects which the frequent visits, the physician's attention, and the whole aura of the clinical study had upon the patients.

Vitally important, too, is the fact that in this trial *q.i.d.* medication meant every 6 hours and not 4 times in the day. These observations should be considered when comparing the obviously superior performance of the study medications to previous therapy.

On medication dose acceptability 5 patients were rated as tolerating both study medications equally well. Fenoprofen was rated as better tolerated in the remaining 5 patients.

CONCLUSIONS

In a limited number of patients, but with an in-depth clinical trial, both fenoprofen and aspirin have been found to be similarly effective agents in the treatment of rheumatoid arthritis. The equally beneficial effects of these two medications have been obtained with an average daily dose of 2,1 g fenoprofen as compared with 4,5 g aspirin. No significant changes in the selected laboratory tests have been observed with either study drug. Patients reported twice as many side-effect occurrences with aspirin as compared with fenoprofen. No drug-related side-effects were attributed to fenoprofen therapy.

Some of the aspects of trial protocol, experimental design and assessment indices have been stressed. Measurement in the rheumatic diseases remains problematical and is at best based on quantifiable subjective and objective parameters. In the face of statistical evidence in this trial, one was perhaps most impressed by the necessity to measure pain—a symptom more accurately measurable than at first thought.[16] Pain is measured in terms of its relief,[17] and it is analgesia in rheumatology which the patient seeks and the doctor most easily recognises and records.

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