COMBINATION THERAPY WITH NAPROXEN AND ASPIRIN IN RHEUMATOID ARTHRITIS

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Thirty-six patients with rheumatoid arthritis were studied to determine the effectiveness and safety of combined therapy with naproxen and aspirin. An 8-week double-blind crossover trial was performed in which naproxen and placebo were administered on a background of constant-dose aspirin. Combination therapy was demonstrated to be more effective than aspirin alone. Tolerance of the two regimens was comparable.

The protocols of clinical trials designed to assess the antiinflammatory activity of new drugs for the treatment of rheumatoid arthritis (RA) customarily proscribe the co-administration of other effective antiarthritic compounds. The banning of background therapy undoubtedly results in a simpler experiment and facilitates the detection of activity. Because multiple drugs are so commonly used in rheumatologic therapy, such exclusions of routine drugs preclude those trials that would answer the clinician's most pertinent question about a new agent, namely: What are its safety and efficacy when administered as part of the overall therapeutic package?

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Because aspirin remains the keystone of antiinflammatory drug therapy in RA, it is relevant to define the therapeutic results achieved by the new agent when its use is superimposed on ongoing treatment with aspirin. The demonstrated pharmacokinetic interactions between aspirin and other nonsteroidal antiinflammatory agents render any simplistic prediction of additivity highly questionable.

Naproxen [*d*-2-(6'-methoxy-2'-naphthyl) proprionic acid, Naprosyn, Syntex Labs, Palo Alto, California] is an arylalkanoic acid derivative that shows considerable promise in the treatment of RA and has been widely tested in clinical trials. In a dose of 250 mg twice daily its activity has been reported to be at least comparable to that of aspirin (1,2) and indomethacin (3) while being better tolerated than either of these agents. The present study was designed to determine if the superimposition of naproxen therapy upon a fixed maintenance dose of aspirin enhanced the therapeutic result or was detrimental to tolerance or safety.

MATERIALS AND METHODS

Adult patients with classic or definite RA (4) and without serious complicating illnesses were studied. They were required to have been on continuous aspirin therapy for at least 3 months, the last month at a constant dose, and still to manifest continuing disease activity such that introduction of additional nonsteroidal antiinflammatory therapy was indicated. This baseline aspirin dose had been arrived at by prior titration to tolerance and thus varied between individual patients. Patients on stable corticosteroid or gold salt regi-

mens could participate but were required to remain on the same fixed maintenance doses throughout the study. Informed consent was obtained after the nature of the study, including the use of placebo, had been fully explained.

The study design was a double-blind crossover comparison of naproxen tablets, 250 mg twice daily, and an indistinguishable lactose placebo. Prior aspirin therapy was continued at the prestudy dose with the investigational therapy superimposed on this regimen. If other nonsteroidal agents had been used, these were discontinued before the trial. The 8-week trial period consisted of 4 consecutive weeks each on naproxen and placebo, assigned in randomized sequence. If side effects developed or if the patient or investigator considered that the drug regimen was not providing adequate symptom control before the end of the first 4 weeks, the patient was advanced to the test compound for the second half of the study; if such events occurred in the second 4 weeks, the trial was terminated prematurely.

Clinical assessments were made at the beginning of the trial and every 2 weeks thereafter (or more frequently if clinically indicated or in the case of premature termination). Disease-related symptoms and signs were evaluated by the standard methods introduced by the Cooperating Clinics Committee of the American Rheumatism Association (5).

At the end of the trial the patients and the observer independently recorded their own impressions of which phase of the study had resulted in better symptom control. The occurrence of adverse drug experiences was monitored by a specific inquiry to the patient with regard to 34 listed symptoms followed by a request for details of additional complaints. A battery of laboratory tests including hemogram, alkaline phosphatase, cholesterol, bilirubin, albumin, globulin, total lipids, SGOT, LDH, creatinine, glucose, BUN, uric acid, and urinalysis was performed at the beginning, crossover point, and end of the trial. Stools were tested for occult blood by the Hemoccult method at each visit.

At the end of the double-blind trial patients who reported benefit from addition of naproxen to their therapeutic program were invited to continue treatment in an open trial.

RESULTS

There were 29 women and 7 men enrolled in the trial. The mean age was 43 years and the average duration of disease 9.3 years. Thirty patients had positive latex tests for rheumatoid factor. Over 80% of the patients were categorized as being in anatomic stage II, functional class II; most of the remainder were either in functional class III, anatomic stage III, or both. Analysis of demographic and disease activity characteristics as recorded at induction into the trial showed that the randomization procedure had resulted in two comparable sequence groups.

The background salicylate dose ranged from 1.3 to 5.2 g/day with both mean and median doses of 3.25 g/day. In addition 9 patients continued their maintenance prednisone therapy (5–10 mg/day), and 3 others continued on gold treatment (50 mg/month after initial loading with 0.5–1.0 g).

Premature Discontinuation

All 36 patients received both test drugs, a procedure that allowed valid comparative analyses. As sanctioned by the protocol, 2 patients prematurely discontinued while taking naproxen and aspirin and 2 others while taking placebo and aspirin because of suspected adverse reactions.

A 26-year-old man, whose background therapy consisted of aspirin, 4.8 g/day, and prednisone, 7.5 mg/day, had suffered from heartburn but did not have a history of gastrointestinal bleeding or peptic ulceration. After naproxen was begun his dyspepsia increased, and 10 days later he noted a black stool without symptoms of hypovolemia. He was seen the following day, at which time the stools were normal in color but showed the presence of occult blood. Hematocrit had fallen from baseline values of 41 vol% to 36 vol%. The investigational drug was discontinued and there was no further indication of blood loss. Upper gastrointestinal x-rays were normal.

A 54-year-old woman noted heartburn after 2 weeks of naproxen treatment. Therapy was discontinued although there was no evidence of blood loss and upper gastrointestinal x-rays were normal. She later received open naproxen therapy without ill effects. Placebo was discontinued because of severe headaches in one patient, and because of buccal ulcers in the other.

Because the therapeutic regimen was not providing satisfactory control of their disease, 17 additional patients availed themselves of the opportunity to terminate a phase of the study prematurely: 2 patients did so during naproxen plus aspirin therapy, 13 during the placebo plus aspirin phase, and 2 during both phases. This difference in dropout rate is statistically significant ($P = 0.02$ by McNemar's test) (6).

Efficacy Evaluation

One of the advantages of crossover design in drug trials is the opportunity it affords for obtaining an overall evaluation of the relative values of two comparative regimens for each individual. Both patients and observer independently scored each treatment sequence as "much better than," "better than," or "equal to" the other. Figure 1 indicates that in a significant majority of cases neither the patients nor the observer had any difficulty in establishing that the addition of naproxen im-

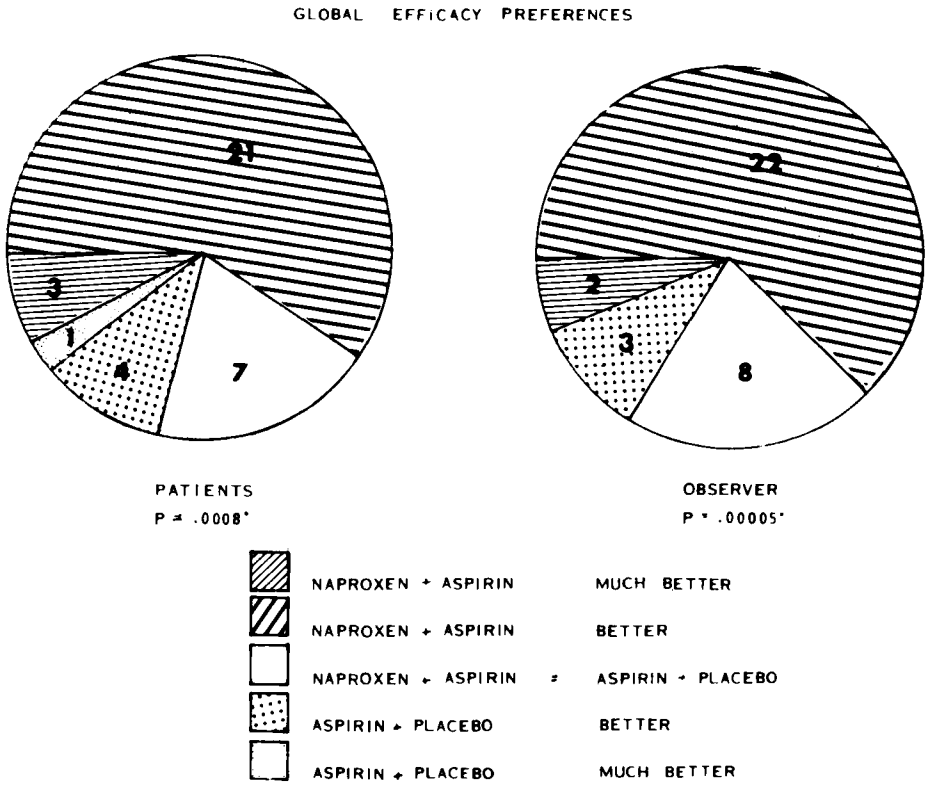

Fig 1. *Overall preferences as independently expressed by the patients and the observer at the end of each trial.*

proved disease control. Combination therapy with naproxen and aspirin was selected in 24 cases, and aspirin was chosen by 5 patients but in only 3 cases by the observer. The observer made no choice in 1 case because he considered one treatment period to have been too short in duration.

Dropouts for inadequate efficacy were not discouraged because differential attrition is itself a useful index of drug activity. Permitting patients to drop out, however, complicates the evaluation of data obtained later in the study. Of the 36 patients who entered, 30 completed the full 4 weeks of combined therapy; only 19 completed the entire period of aspirin–placebo treatment. The difference is accounted for completely by patients who discontinued placebo treatment because it was not providing improved disease control. Because patients remaining in the trial beyond the first visit in each phase were likely to be doing better than those who dropped out, a systematic bias was introduced that made any comparison of rheumatic disease indicators at the end of the trial periods of questionable validity. To ensure comparability, quantitative observations of disease-related signs and symptoms presented in Table 1 were those recorded at the end of 2 weeks of naproxen plus aspirin and 2 weeks of aspirin plus placebo therapy.

To approximate closely a practice situation, patients were permitted to continue maintenance gold or corticoid therapy. Likewise, the aspirin dose, although kept constant during the trial, was not fixed for all patients but rather was individualized by prior titration to tolerance. Because of these variations in concomitant medication, preliminary analyses were performed to examine the homogeneity of the results. The degree of improvement, as measured by naproxen-placebo differences in each of the recorded measures of disease activity, was compared for patients who were receiving prednisone and for those who were not. Steroid patients showed more improvement in some indicators when naproxen was added, but less in others. The difference between the two groups was small and did not approach statistical significance for any parameter.

The authors also ascertained the relationship of aspirin dose to naproxen-placebo differences in the measures of disease activity and to the overall patient and observer efficacy preferences. Kendall's nonparametric correlation coefficients were computed. That

Table 1. *Comparison of Disease-Related Signs and Symptoms During Each Study Phase*

	Naproxen + Aspirin	Aspirin + Placebo	Difference	*P* Value Parametric (7)	*P* Value Wilcoxon (8)
Morning stiffness (ARA decile class) (5)	6.0	6.8	0.8	0.008	0.018
Number of joints involved	28.6	31.0	2.4	0.26	0.34
Number of joints swollen	20.4	22.3	1.9	0.35	0.23
50-foot walk (seconds)	11.1	11.8	0.7	0.002	0.002
Grip strength (mm Hg)	125.0	112.0	13.0	0.062	0.013

all these correlations were negative suggested that patients receiving the largest aspirin dose tended to show the least improvement when naproxen was added. Individual values scattered widely, however, and the computed correlations were of a low order, with coefficients ranging from −0.03 to −0.35.

These preliminary analyses supported the pooling of the entire study population in the final analysis, the results of which are presented in Table 1. All indicators favored the period of combined therapy over the phase without naproxen. The observed differences of the means were rather modest, although morning stiffness, 50-foot walking time, and grip strength attained statistical significance.

Tolerance

The only potentially serious adverse effect, a probable case of bleeding from the upper gastrointestinal tract, has been described previously. Predictably, probed questioning elicited many other complaints. One or more complaints were reported by 17 patients during combined aspirin and naproxen administration, and by 21 patients during the aspirin plus placebo phase. These complaints were not thought to be of clinical importance and did not differ significantly in nature, severity, or frequency between the two treatment regimens.

Long-Term Open Study

Twenty-nine of the 36 patients elected to go into the long-term open trial and 20 decided to continue on combined therapy. In approximately half of the cases, the naproxen dose has been increased to 750 mg/day. The current therapeutic response is judged to be good or excellent in 15 patients.

Neither during the double-blind study nor the open follow-up trial were any changes judged to be significant in the laboratory tests of organ function. With the single exception already mentioned, occult blood was not found in any of the fecal samples.

DISCUSSION

In experimental inflammation in rodents, the concurrent administration of aspirin and indomethacin (9,10), phenylbutazone and aspirin (10), or phenylbutazone and indomethacin (10) was no more effective in relieving inflammation than was each drug alone. Indeed, in the adjuvant arthritis model, indomethacin and aspirin actually antagonized each other (11). The mechanism underlying these observations is unclear but certain data point to a pharmacokinetic interaction. Yesair and associates (12) demonstrated that simultaneous administration of salicylic acid markedly decreased the plasma concentration of ^{14}C-labeled indomethacin, enhanced hepatobiliary–fecal excretion, and modified tissue concentrations. Chignell and Starkweather (13) postulated that this effect was the result of an alteration of indomethacin binding sites on albumin by the salicylate.

Studies in man have also shown that concurrent administration of aspirin reduced the blood concentration of indomethacin and fenoprofen (14) and of naproxen (15). The plasma level differences were not large, the size of the difference varied in the several reports, and some observers have failed to show significant falls in indomethacin levels when aspirin was taken concurrently. In any case, to demonstrate that a pharmacokinetic interaction is of clinical relevance and more than a curiosity, trials (using multiple agents) must be undertaken in arthritis patients.

Several attempts to show an additive effect of aspirin and indomethacin have been reported. The trial conducted by the Cooperating Clinics Committee of the ARA (16) in 136 patients with rheumatoid arthritis showed that indomethacin was not superior to placebo,

but the patients were allowed aspirin ad libitum and variations in aspirin dose may well have confounded the results. In a more recent report Brooks *et al* (17) compared the clinical effect of concurrent indomethacin and aspirin treatment in 20 patients with rheumatoid arthritis. Patients were given indomethacin, 100 mg/day, soluble aspirin, 4 g/day, and the two drugs together in a random order. The three drug regimens did not yield significantly different results, although patient preferences favored indomethacin alone by a small margin. One would conclude that in patients receiving 4 g/day of aspirin the addition of indomethacin does not lead to better symptom control. The study did not examine whether patients receiving smaller doses of aspirin would benefit by the introduction of indomethacin; the present authors believe this to be a valid question. Many patients do not tolerate a 4 g/day dose; indeed 3 of 20 patients in the Brooks study had to drop out before completing the 2-week aspirin treatment period.

The trial reported here was designed to bridge the gap between the two studies described above. Clinical relevance was maintained by administering a dose of aspirin arrived at by prior individualized titration to tolerance, but the confounding effect that would have resulted from allowing variations in aspirin dose *during* the trial was avoided. The results were clear-cut. Analysis of patient preferences, perhaps the most sensitive criterion available in assessing the real benefits of antirheumatic drugs (18), showed that patients selected the combination at a highly significant level. Patients receiving higher doses of aspirin tended to show less incremental improvement with the addition of naproxen, but the low order of correlation did not impair the validity of these general conclusions.

The present study also addressed the fear that the addition of naproxen therapy to a maintenance aspirin regimen might have adverse effects on tolerance or safety. One case of probable upper gastrointestinal bleeding was observed during the double-blind trial in a patient taking naproxen, aspirin, and prednisone. No other significant adverse effect occurred during the study, and analysis of complaints showed no increase during combined therapy. Clinical safety has been further substantiated in the open therapy experience that followed and is still in progress.

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