Naproxen in osteoarthritis

Double-blind crossover trial

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SUMMARY In this double-blind crossover trial, naproxen (750 mg/day) was compared to placebo for the treatment of osteoarthritis of the hip and knee. Patients were randomly assigned to treatment with either naproxen or placebo for 4 weeks and then to treatment with the alternate agent for a second 4-week period. 8 out of 9 objective and subjective measurements of drug efficacy clearly differentiated naproxen from placebo at highly significant levels ($P=0.0001$ to 0.0004). Patient daily check lists of osteoarthrotic symptoms also showed a statistically significant difference between naproxen and placebo therapy. Both physicians and patients, when asked to give a 'final drug preference', showed a significant preference for naproxen over placebo. In general, the incidence of side effects was low and approximately the same for both naproxen and placebo. Laboratory assessments showed little difference between groups. The trial showed naproxen to be an effective and well tolerated drug for the treatment of osteoarthritis of the hip and knee.

Osteoarthritis is a very common disorder characterised by cartilaginous degeneration, osteophytosis, and deformity of the joint margins. Weight-bearing joints are frequently affected. Studies have shown that by the age of 40, 90% of all persons have degenerative changes in the weight-bearing joints (Lowman, 1955).

Aspirin has been the cornerstone of drug therapy for osteoarthritis. However, because of its known side effects, research has been directed toward the development of new nonsteroidal anti-inflammatory agents with low toxicity. Naproxen (Naprosyn) is one of these newer agents. Clinical studies have shown it to be an effective, well tolerated drug for the treatment of rheumatoid arthritis (Helby-Peterson *et al.*, 1973; Hill *et al.*, 1974; Bowers *et al.*, 1975; Huskisson *et al.*, 1976). In addition, earlier studies have suggested that naproxen is also effective for the relief of the signs and symptoms of osteoarthritis (Cochrane, 1973; Kageyama, 1973; Tanaka *et al.*, 1976). Accordingly, this study was designed to further evaluate the efficacy and tolerance of nap-

roxen for the treatment of osteoarthritis of the two commonly affected weight-bearing joints, the hip and knee.

Methods

SELECTION OF PATIENTS

Patients who had actively symptomatic osteoarthritis of the hip and knee were selected using three admission criteria: (1) pain on passive motion or tenderness on pressure in at least one hip or knee; (2) roentgen evidence of osteoarthritis in at least one symptomatically affected hip or knee, and (3) an increase in hip and/or knee pain during an initial single-blind placebo period. Patients who had a concomitant disease which might cause inflammation of joints, those with a history of gastrointestinal bleeding or other serious haematological, hepatic, or renal disorders, and pregnant or lactating women were excluded from the trial.

Eighty-nine patients were admitted to the double-blind phase of the study; 59 females and 30 males. The mean age of the group was 66.4 years. Duration of osteoarthrotic symptoms before admission to the trial ranged from 3 months to 480 months, mean 9

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months. 79 took part in both phases of the crossover and were evaluated. 3 were excluded because of frequent unauthorised use of concomitant analgesic medication (aspirin, codeine, and/or d-propoxyphene). The remaining 7 patients did not enter the second phase of the trial: 5 withdrew during placebo administration (2 because of excessive osteoarthrotic symptoms, 2 because of suspected side effects, and 1 because of an intercurrent urinary tract infection); 2 withdrew during naproxen administration because of nausea and dyspepsia.

STUDY DESIGN

This multicentre study was a double-blind crossover comparison of naproxen and placebo in osteoarthritis of the hip and knee. At the beginning of the trial prior anti-inflammatory and analgesic medication was abruptly withdrawn, and patients entered into a single-blind baseline period on placebo. An increase in osteoarthrotic symptoms within the ensuing 3 to 14 days was taken to indicate the presence of active osteoarthritis. After a patient showed evidence of increased symptoms, random assignment was made to treatment with either naproxen, 750 mg/day (375 mg bid), or placebo on a double-blind basis. Patients continued therapy for 4 weeks and then were crossed over to treatment with the alternate agent for a second 4-week period. If symptoms worsened or side effects developed before the first 4 weeks of the double-blind trial were completed, early advancement to the second half of the crossover was permitted. Early withdrawal from the second phase of the crossover was similarly

allowed. Other analgesic or anti-inflammatory medication was not permitted.

EFFICACY EVALUATION

Clinical assessments were made at baseline (end of single-blind placebo period) and at 2-week intervals thereafter. Each affected hip and knee was evaluated independently for a variety of disease-related signs and symptoms (e.g. pain on passive motion or tenderness on compression). In addition, a number of variables were measured in order to evaluate the patient's ability to function (e.g., mean 25-foot walking time). Objective measurements were quantified when possible, and for the others a system of scoring was used so that data from the various treatment centres would be coded uniformly (Tables 1, 2). When the scale was 0-4: 0=none; 1=minimal or borderline; 2=mild to moderate; 3=moderate to severe; 4=incapacitating; and when the scale was 0-5: 1=easy and asymptomatic; 2=easy but causes mild discomfort; 3=possible but moderately difficult or painful; 4=possible but very difficult or painful; 5=impossible. Range of motion in the knee was assessed goniometrically using the maximum range of flexion-extension recorded with the patient in the prone position.

At the final double-blind examination the physician and then the patient independently indicated whether one phase of the crossover was much better, better, or no different than the other for the relief of symptoms. The physician then also evaluated the overall side effects for each phase of the crossover (none, mild, moderate, or severe). In addition, patients were requested to complete a daily checklist

Table 1 *Measurements of drug efficacy*

Parameter (units)	n*	Means		P†
		Naproxen	Placebo	
Hip joints: painful and/or tender (0=none, 4=incapacitating)	31	1.66	2.29	0.0004
Knee joints: painful and/or tender (0=none, 4=incapacitating)	58	1.03	1.82	<0.0001
Knee joints: swelling and/or effusion (0=none, 4=incapacitating)	58	0.45	0.58	0.1553
Activity of daily living (1=easy, 5=impossible)	79	2.65	3.38	<0.0001
Physician's assessment of disease activity (0=none, 4=incapacitating)	76	1.89	2.47	<0.0001
Patients' assessment of disease activity (0=none, 4=incapacitating)	77	1.90	2.61	<0.0001
Duration of morning stiffness (min) 999=all day	79	‡	‡	<0.0001
25-foot walking time (s) (average of two trials)	78	7.14	8.10	<0.0001
Knee joints: range of motion (degrees). Averages if both were involved at baseline	57	101.94	94.27	0.0002

*Out of a total of 79 patients evaluated; includes all available data.

†2-tailed probability using Wilcoxon-Mann-Whitney test (Koch, 1972).

‡Means are not meaningful because some patients reported 'all day' as 999.

Table 2 Average daily symptom scores from patient daily checklist

Parameter (units)	n*	Means		Pt
		Naproxen	Placebo	
Pain with activity (0 = none, 5 = incapacitating)	73	2.93	3.41	<0.0001
Pain at night (0 = none, 5 = extremely severe)	73	2.46	2.91	<0.0001
Getting in and out of car (1 = no discomfort, 5 = impossible)	73	2.33	2.71	<0.0001
Tying shoes (1 = no discomfort, 5 = impossible)	66	2.06	2.30	0.0006
Morning stiffness (0 = none, 7 = > 2 h)	72	3.71	4.33	<0.0001
Walking (one block) (1 = no discomfort, 5 = impossible)	73	2.65	3.06	<0.0001

*Out of a total of 79 patients evaluated; includes all available data. 6 patients failed to complete the checklist.
†2-tailed probability using Wilcoxon-Mann-Whitney test (Koch, 1972).

grading 6 disease-related variables (e.g. duration of morning stiffness).

SAFETY EVALUATION

At the beginning of the trial and every 4 weeks during the trial, the following laboratory investigations were performed: complete blood count, routine urinalysis, alkaline phosphatase, total cholesterol, total bilirubin, total protein, albumin level, SGOT, LDH, serum creatinine, blood glucose, blood urea nitrogen, serum uric acid, calcium, phosphorus, sodium, potassium, and chloride. At each visit stools were tested for occult blood using the Hemocult slide method. At each examination the patients were asked if they had experienced any symptoms which they thought might be caused by the medication.

Results

RESPONSE TO DRUG THERAPY

Analysis of the variables studied showed naproxen to be effective in relieving the symptoms of osteoarthritis. 8 out of the 9 objective and subjective measurements of drug efficacy given in Table 1 clearly differentiated naproxen from placebo at highly significant levels (P=0.0001 to 0.004). Pain on motion or tenderness was reduced, activities of daily living were easier, the overall severity of symptoms was less, the duration of morning stiffness was reduced, and walking time improved. Range of motion was also significantly improved for affected knees. Swelling, while sometimes present in the affected knee joints, was generally absent or mild and thus presented limited potential for statistical discrimination. Although the naproxen-placebo difference for this variable failed to reach statistical significance, the difference favoured naproxen.

The patient daily checklists also helped to evaluate drug efficacy. As Table 2 shows, the findings closely paralleled those in Table 1. All variables showed a statistically significant difference between naproxen and placebo therapy. Naproxen reduced the patient's pain with activity, nocturnal pain, morning stiffness, and functional impairment as judged by the patient's ability to get in and out of a car, walk one block, or tie shoelaces.

Of the 79 patients who participated in both phases of the trial, 77 completed the naproxen phase, and 62 completed the placebo phase. 2 did not complete the naproxen phase because of inadequate disease control. 37 failed to complete the placebo phase of the study: 35 because of inadequate disease control and 2 because of side effects. The difference between the number who prematurely discontinued placebo (37) and the number who discontinued naproxen (2) was statistically significant (P=0.0001).

Finally, the two drugs were evaluated using the physicians' and patients' assessment of 'final drug preferences'. Subjective forms of assessment such as this have been found to be sensitive indicators of drug efficacy (Lee *et al.*, 1973, 1976). While still under double-blind conditions, the investigator considered the naproxen period better or much better in 28 instances, the placebo period better or much better in 12 instances, the two drugs equal in nine instances. This difference was statistically significant (P<0.00001). The patients' own preferences closely paralleled those of the physician (Fig.).

SIDE EFFECTS

Two of the 89 patients who were originally admitted to the study withdrew in the first phase of the trial due to mild gastrointestinal side effects (nausea and dyspepsia) while on naproxen. Neither was included in the efficacy evaluations. One of these patients

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Fig. Physicians' and patients' 'final drug preference' given while still under double-blind conditions.

*Preference missing for 1 patient.

entered the study with a history of gastric intolerance to other nonsteroidal anti-inflammatory agents.

Four of the original 89 patients admitted to the study withdrew or terminated one phase of the crossover prematurely because of suspected side effects while receiving placebo. One patient (with pre-existing macular degeneration) withdrew because of blurred vision, a second because of abdominal pain and difficulty in concentrating. Neither was included in the efficacy analysis.

An additional 2 patients complained of abdominal pain, nausea, vomiting, and/or dyspepsia during placebo administration. Both patients were prematurely crossed over to the second phase of the trial and completed 4 weeks of naproxen therapy without developing side effects. Since data from both phases of the trial were available for these 2 patients, they were among the 79 patients included in the efficacy analysis. In general, the incidence of side effects was low and approximately the same for both naproxen and placebo (Table 3).

Hemoccult tests for occult blood were negative in 303 of the 310 specimens tested. Three specimens were positive during placebo administration before naproxen therapy, and three were positive at baseline or during the pretrial placebo washout period. The one positive Hemoccult test during naproxen therapy occurred in a patient who had a positive test during the pretrial period and two positive tests during placebo administration. This patient's test was positive at the first visit on naproxen but was negative at the second visit. There were no clinical or haematological signs of anaemia.

No major abnormalities due to drug therapy were seen. Although there were occasional deviations

from the normal range, the mean laboratory values for all patients were normal throughout the trial.

Discussion

Osteoarthritis is the most common form of joint disease seen by the practising physician. As yet, however, control of its pathogenesis is beyond the grasp of current understanding, the treatment therefore remains symptomatic rather than specific. The actual choice of treatment depends on the extent of discomfort or disability. Mild symptoms can often be adequately treated with reassurance, rest, and physical therapy. On the other hand, more severe symptoms require drug therapy. Active treatment is

Table 3 Per cent of visits at which complaints were recorded during naproxen and placebo administration

Complaint	Naproxen*	Placebo*
Gastrointestinal tract		
Nausea and vomiting	3.0	5.9
Abdominal pain	4.2	5.1
Dyspepsia	1.2	1.5
Diarrhoea	2.4	5.1
Constipation	3.0	2.9
Decreased appetite	1.8	0
Central nervous system		
Headaches	1.8	7.4
Dizziness	3.0	0.7
Mental confusion	0	1.5
Vertigo	1.8	0
Visual disturbance	1.8	1.5
Other		
Palpitations	0	1.5
Itching	0.6	2.9
Oedema	1.8	0.7

*Naproxen = 168 patient visits; placebo = 136 patient visits.

essential not only for the immediate benefits of increased comfort and function, but for retarding disease progression and protecting contralateral joints which may be exposed to increased stress (Moskowitz, 1972a).

While osteoarthritis is primarily a degenerative process, inflammatory changes have been noted in some patients (Crain, 1961; Ehrlich, 1975; Kellgren and Moore, 1952). Inflammatory synovitis is frequently found both clinically and at surgery, and while this synovitis is less severe than that seen in rheumatoid arthritis it may still contribute significantly to the patient's symptoms. Whatever the cause of this inflammation, anti-inflammatory analgesic drugs are often more beneficial than simple analgesics alone.

Aspirin has been used as the main drug therapy in osteoarthritis. However, osteoarthritis is a disorder of older people whose concomitant illnesses may include marginal cardiovascular and cerebrovascular function with frequent impairment of vision and hearing. As a result, these patients are more likely to develop aspirin toxicity (Moskowitz, 1972b).

In this study naproxen was found to be an effective and well tolerated drug, supporting the findings of Aagaard (1975) in a previous double-blind crossover study of naproxen (500 mg/day) versus placebo. In that study naproxen was shown to cause statistically significant improvement in pain at rest, walking time, and pain on effort. Side effects were found to be slight and occurred in approximately the same frequency during naproxen and placebo administration.

The results of our study suggest that naproxen is a potentially useful alternative to aspirin for the management of osteoarthritis. Its 13-hour half-life makes twice-a-day dosage possible, and offers an additional benefit to some patients.

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