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Harris H. Macllwain

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# Enteric-Coated Fenoprofen in Large-Joint Osteoarthritis\*

Gilbert B. Bluhm, MD,<sup>†</sup> Harris H. MacIlwain, MD,<sup>‡</sup> and Walter W. Offen, PhD<sup>§</sup>

*Enteric-coated fenoprofen was compared with standard fenoprofen (Nalfon<sup>®</sup>, Dista, Indianapolis, IN) in a randomized, double-blind, parallel, three-month trial of 113 outpatients (mean age, 64 years) with large-joint osteoarthritis. A previous study showed that enteric coating of fenoprofen reduces gastrointestinal microbleeding and may offer a safety advantage. Both treatments provided statistically significant improvement in pain measures (tenderness on pressure, pain at rest, pain with weight-bearing activity, and pain on passive motion). Adverse experiences were similar with both treatments and of an expected type, severity, and incidence for nonsteroidal anti-inflammatory drugs. Enteric-coated fenoprofen was found to be as effective and safe as standard fenoprofen for large-joint osteoarthritis. (Henry Ford Hosp Med J 1988;36:56-60)*

Fenoprofen calcium (Nalfon<sup>®</sup>, Dista, Indianapolis, IN) is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Although its exact mode of action is not known, inhibition of prostaglandin synthetase is probably involved. As an NSAID, fenoprofen has proven to be effective in the treatment of rheumatoid arthritis and large-joint osteoarthritis (1). In patients with osteoarthritis, the anti-inflammatory and analgesic effects of fenoprofen have been demonstrated by a reduction in the common measures of disease activity. Efficacy and safety of fenoprofen compare favorably with those of other agents used to treat osteoarthritis, such as aspirin (2-4), indomethacin (5), ibuprofen (6), and sulindac (7). However, fenoprofen, like other NSAIDs, is known to produce gastrointestinal (GI) irritation, bleeding, and other GI symptoms (8). While studies have shown that fenoprofen is safer than aspirin and no long-term clinical risks are associated with its use for treatment of osteoarthritis (8-10), it is important to minimize risks of GI bleeding.

To protect the mucosal membrane of the stomach from irritation produced by aspirin and NSAIDs, enteric coatings have been developed that do not change the biologic half-life of the drug (11). A recent study showed that an enteric-coated form of fenoprofen reduced GI microbleeding significantly (12). The bioavailability of the two formulations is equal (data on file, Lilly Research Laboratories, Indianapolis, IN).

The purpose of this study was to compare the two formulations to determine whether the enteric-coated form is as effective and safe as standard fenoprofen calcium. If so, enteric-coated fenoprofen may have fewer adverse GI effects than fenoprofen calcium when used for the long-term treatment of large-joint osteoarthritis.

## Materials and Methods

### Patient population

Male and female ambulatory outpatients, 18 years or older, with active osteoarthritis were selected for the study. All patients

were taking fenoprofen calcium for their disease condition immediately before the trial began. Six independent clinical centers participated in the study.

The presence of osteoarthritis was established by the following diagnostic criteria: roentgenological evidence of large-joint (hip or knee) osteoarthritis and one or more of the following signs and symptoms of osteoarthritis: tenderness on pressure, pain on passive motion, pain with weight-bearing activity, or pain at rest. The symptomatic knee or hip was the cardinal joint evaluated.

Patients were excluded from the study if they had:

- evidence of rheumatoid arthritis, lupus erythematosus, psoriasis, syphilitic neuropathy, or metabolic bone disease;
- cardiac, renal, hepatic, gastrointestinal, or other serious diseases that would be exacerbated by the study medications or interfere with study evaluation;
- hypersensitivity to fenoprofen calcium, aspirin, or other drugs;
- history of alcohol or drug abuse within one year;
- clinically significant psychiatric problems;
- inability to take oral medications.

Patients with serious diseases were accepted into the study only if the investigator determined that the condition(s) would not interfere with the study evaluation. Women of childbearing age were included if they were on an effective contraceptive program approved by the investigator. The study protocol was

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\*This was a six-center study. In addition to the coauthors, the senior investigators included Dr. M.C. Austin, Newport Beach, CA; Dr. J.S. Habros, Phoenix Arthritis Center, Phoenix, AZ; Dr. M.D. Heller, Arthritis Associates, Lynnfield, MA; and Dr. S.D. Solomon, Arthritis and Rheumatic Disease Associates, Cherry Hill, NJ.

<sup>†</sup>Department of Rheumatology, Henry Ford Hospital.

<sup>‡</sup>MacIlwain & Silverfield, MDs, PA, Habana Medical Center, Tampa, FL.

<sup>§</sup>Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN.

Address correspondence to Dr. Bluhm, Department of Rheumatology, Henry Ford Hospital, 2799 W Grand Blvd., Detroit, MI 48202.

approved by the institutional review boards at each of the participating centers, and all patients signed an informed consent form.

### Study design

The study was a randomized, double-blind, parallel trial conducted at six centers by independent investigators. The study began with a two-week placebo qualification period during which patients were withdrawn from fenoprofen calcium to demonstrate active osteoarthritis symptoms and to eliminate apparent placebo reactors by indicating the need for active medication. During this time, patients were allowed to take acetaminophen (500 mg) if they required an analgesic to relieve pain. If the symptoms of osteoarthritis became unbearable, the placebo period was shortened and the patient entered the active treatment phase before the two-week period ended.

After this two-week period, eligible patients were randomly allocated to one of two treatment groups: fenoprofen calcium, 600 mg, or enteric-coated fenoprofen, 600 mg. Patients who entered the active treatment phase received one of the two medications four times a day for 12 consecutive weeks. No adjustments in dosage were permitted, and patients were not allowed to switch formulations. Compliance was assessed at each visit by counting capsules and by measuring serum fenoprofen calcium concentrations. Additional analgesics were not permitted during the active treatment period.

Patients were evaluated by the investigator at four regularly scheduled visits during the three-month period. At each visit, the investigator evaluated clinical symptoms of osteoarthritis, recorded any adverse events, dispensed the study medication, and collected blood or urine samples. At the conclusion of the final visit, the investigator prepared a final summary report for each patient.

### Measures of efficacy

Four pain parameters were used to measure the patient's response to the study medication: tenderness on pressure and pain on passive motion, which were evaluated directly by the clinician, and pain at rest and pain with weight-bearing activity, which were evaluated through interview of the patient. At each visit, the investigator rated these parameters on a four-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. To minimize variation, the same investigator evaluated the same patient at each visit at approximately the same time of day.

### Statistical analysis

The four efficacy variables were analyzed in two ways. First, changes from baseline to endpoint were analyzed by analysis of variance (ANOVA) on the ranks of the data. ANOVA was performed twice, first on all data and then on evaluable data alone. Baseline was the visit at which the treatment phase began, and endpoint was the last visit for which data were collected. ANOVA included three independent variables: investigator, drugs, and their interaction. In addition, a Wilcoxon rank sum test, which does not account for any differences due to investigators, was performed on the four efficacy variables, and a Wilcoxon signed rank test was used to analyze the two treatment

groups individually for any significant changes within the group. The second form of analysis used the same statistical techniques as the first, but in this case changes from baseline to each of the three months of the study were analyzed separately.

A standard Pearson chi-square test was used to analyze three primary reasons for termination from the study: protocol completed, lack of efficacy, or adverse events. For this study, statistical significance was defined as  $P \leq 0.05$ . All treatment comparisons were two-tailed.

### Laboratory studies

Samples were collected at the beginning of the placebo qualification period and at the end of the last visit for blood chemistry profiles, hematological tests, and urinalysis. Compliance blood samples were drawn after each of the three months of treatment.

### Adverse events

An adverse event was defined as any undesired occurrence during treatment with the medication whether or not it was considered drug-related. These included any deaths or hospitalizations, withdrawal from the study due to a serious adverse event, change in renal function or proteinuria, melena or GI perforation, obvious weight gain or edema, or jaundice or hepatic damage. Adverse events were elicited by interview at each visit. All adverse events were reported by each investigator as to duration, severity, and outcome.

## Results

### Patient population

A total of 131 patients were screened for entry into the study. Of the 113 who qualified for active therapy, 55 were randomly allocated to receive enteric-coated fenoprofen and 58 to receive fenoprofen calcium. Another patient, who qualified for active therapy and participated in the study, was excluded because his data were unavailable at the time of analysis. Distribution of the 113 patients among the six investigators and two treatment groups was relatively well balanced. The differences between the two treatment groups were not statistically significant for any of the variables described below.

Thirty-nine (71%) of the patients receiving enteric-coated fenoprofen and 45 (78%) receiving fenoprofen calcium were women. Forty-one (75%) patients receiving enteric-coated fenoprofen and 45 (78%) receiving fenoprofen calcium were white; 14 (25%) patients receiving enteric-coated fenoprofen and 13 (22%) receiving fenoprofen calcium were black. The knee was the involved osteoarthritic joint in 43 patients receiving enteric-coated fenoprofen and in 50 receiving fenoprofen calcium. The hip was involved in 12 patients receiving enteric-coated fenoprofen and in eight receiving fenoprofen calcium.

Age distribution of patients in the two treatment groups is given in Table 1. The mean age was 64 years in both groups. In the group receiving enteric-coated fenoprofen, 48 (87%) of 55 were between 51 and 80 years old. In the group receiving fenoprofen calcium, 50 (86%) of 58 were in this age range.

On admission to the study, 38 (69%) patients in the enteric-coated fenoprofen group and 45 (78%) in the fenoprofen calcium group listed a current sign, symptom, or illness other than

**Table 1**  
**Age Distribution of Patients with Large-Joint Osteoarthritis Receiving Enteric-Coated Fenoprofen or Standard Fenoprofen Calcium**

Age	Enteric-Coated Fenoprofen (n = 55)	Standard Fenoprofen Calcium (n = 58)
	Number (%) of Patients	Number (%) of Patients
< 30	0	1 (2)
31-40	1 (2)	0
41-50	4 (7)	5 (9)
51-60	16 (29)	13 (22)
61-70	16 (29)	23 (40)
71-80	16 (29)	14 (24)
> 81	2 (4)	2 (3)

osteoarthritis. Forty-one (75%) patients in the enteric-coated fenoprofen group and 45 (78%) in the fenoprofen calcium group reported concomitant drug therapy on admission, which continued throughout the study.

During the placebo qualification period, the number of acetaminophen capsules taken as an analgesic was monitored and then recorded at the start of the treatment phase. The mean number of capsules taken was 31 for patients receiving enteric-coated fenoprofen and 30 for patients receiving fenoprofen calcium.

#### Analysis of efficacy variables

For all efficacy variables, the tests for changes within each individual treatment group were statistically significant ( $P < 0.001$ ) for both the endpoint analysis (Table 2) and the monthly analysis. Thus, patients in both treatment groups experienced improvement in their disease condition.

The primary analysis of efficacy was the endpoint analysis on all data (Table 2). No statistically significant differences were noted between the treatment groups for any of the efficacy measures. Also, the difference at baseline was not significant.

For the secondary analysis of data at each of the three months, the only statistically significant treatment difference occurred during the second month for the variables of pain with weight-bearing activity and pain on passive motion (Table 3). In both instances, the group receiving fenoprofen calcium showed

greater improvement than the group receiving enteric-coated fenoprofen. No statistically significant differences were noted at the first and third months.

Several visits were considered unevaluable for various reasons such as protocol violation, use of other analgesics, or poor compliance. Sixteen (29%) patients receiving enteric-coated fenoprofen and ten (17%) receiving fenoprofen calcium had at least one visit declared unevaluable; however, this difference was not statistically significant. When ANOVA was repeated for the endpoint analysis on evaluable data only, the conclusions did not differ from those for the analysis of all data. No significant differences between treatment groups were observed.

The secondary analysis for each of the three months was also repeated for evaluable data only. Results were similar to those obtained for the analysis of all data, except that differences for the two efficacy variables of pain with weight-bearing activity and pain on passive motion were no longer statistically significant at the second month.

#### Adverse events

The overall incidence of adverse events was similar for the two treatment groups, with 36 (65%) of the patients receiving enteric-coated fenoprofen and 41 (71%) of those receiving standard fenoprofen reporting an adverse event at some time during the study. Events reported by two or more patients in either treatment group consisted of abdominal pain, flatulence, nausea, dyspepsia, diarrhea (not otherwise specified), headache, vomiting, constipation, upper respiratory infection, urinary tract infection (not otherwise specified), nasal congestion, sinusitis, cough, dry mouth, peripheral edema, and potassium deficiency. No statistically significant differences were noted between treatment groups for any of the adverse events reported during the study.

Of the 13 (11.4%) patients who withdrew from the study because of an adverse experience, five had been receiving enteric-coated fenoprofen and eight had been receiving fenoprofen calcium (Table 4). Two patients were withdrawn from the study when they were hospitalized: one had a myocardial infarction, and the other had mild vaginal bleeding resulting from a severe urinary tract infection. One other patient, who was also hospitalized during the study for a urinary tract infection, returned to

**Table 2**  
**Endpoint Analysis of All Data for Four Efficacy Variables on 113 Patients Receiving Enteric-Coated Fenoprofen or Standard Fenoprofen for Treatment of Large-Joint Osteoarthritis**

Variable	Treatment	Number	Baseline*	Endpoint*	Difference*†
Tenderness on pressure	Enteric-coated	55	2.00 ± 0.84	0.69 ± 0.77	1.31 ± 0.90
	Standard	58	2.09 ± 0.76	0.67 ± 0.76	1.41 ± 0.80
Pain at rest	Enteric-coated	55	1.51 ± 0.94	0.62 ± 0.87	0.89 ± 1.08
	Standard	58	1.64 ± 0.93	0.47 ± 0.82	1.17 ± 1.08
Pain with weight-bearing activity	Enteric-coated	55	2.38 ± 0.71	1.45 ± 0.81	0.93 ± 0.90
	Standard	58	2.57 ± 0.60	1.40 ± 0.84	1.17 ± 0.80
Pain on passive motion	Enteric-coated	55	2.00 ± 0.88	0.76 ± 0.79	1.24 ± 0.92
	Standard	58	2.22 ± 0.73	0.79 ± 0.79	1.43 ± 0.82

\*Mean ± standard deviation.

†When the two treatment groups were compared, the P-value of the differences between baseline and endpoint was not significant for any of the four variables. However, within each treatment group the difference between baseline and endpoint was significant ( $P < 0.001$ ) for all four variables.

**Table 3**  
**Second-Month Analysis of All Data for Four Efficacy Variables on Patients Receiving Enteric-Coated Fenoprofen or Standard Fenoprofen for Treatment of Large-Joint Osteoarthritis**

Variable	Treatment	Number	Baseline*	Endpoint*	Difference*	P-value
Tenderness on pressure	Enteric-coated	48	2.00 ± 0.85	0.71 ± 0.58	1.29 ± 0.68	0.322
	Standard	52	2.08 ± 0.76	0.63 ± 0.69	1.44 ± 0.80	
Pain at rest	Enteric-coated	48	1.50 ± 0.92	0.67 ± 0.75	0.83 ± 0.95	0.229
	Standard	52	1.56 ± 0.94	0.46 ± 0.70	1.10 ± 0.98	
Pain with weight-bearing activity	Enteric-coated	48	2.38 ± 0.70	1.40 ± 0.71	0.98 ± 0.86	0.040
	Standard	52	2.52 ± 0.61	1.25 ± 0.71	1.27 ± 0.79	
Pain on passive motion	Enteric-coated	48	1.98 ± 0.91	0.88 ± 0.70	1.10 ± 0.86	0.046
	Standard	52	2.19 ± 0.74	0.73 ± 0.66	1.46 ± 0.80	

\*Mean ± standard deviation.

active study medication after she had recovered and completed the full course of study. No deaths occurred during the study.

### Laboratory results

No adverse events were detected by blood chemistry (including liver and renal function) or hematological tests during the study. No patients withdrew because of hematological events, and no adverse events were associated with WBC counts in any patient.

Fifty-three (96%) of the patients receiving enteric-coated fenoprofen and 54 (93%) receiving standard fenoprofen had adequate serum samples for determination of drug concentrations. The mean serum concentrations (± standard deviation) in the enteric-coated fenoprofen and standard fenoprofen calcium groups were 29.5 ± 15.6 µg/mL and 35.6 ± 19.9 µg/mL, respectively (P = 0.086). However, capsule counts during the study indicated slightly better compliance in patients receiving standard fenoprofen calcium; mean tablets per day were 3.4 in the group receiving enteric-coated fenoprofen and 3.7 in the group receiving standard fenoprofen (P = 0.028), which may largely explain the observed differences in mean serum concentrations.

### Withdrawal from the study

Patients were withdrawn from the study for the following reasons: adverse event (13 patients), lack of efficacy (six patients), patient's decision (one patient), protocol violation (one patient), and lost to follow-up (one patient). The number of patients who completed the study included 44 (80%) from the enteric-coated fenoprofen group and 47 (81%) from the fenoprofen calcium group.

### Discussion

This study was designed to determine whether an enteric-coated form of fenoprofen is as effective and safe as standard fenoprofen. By all four measures of efficacy tested, there were no consistent statistically significant differences between the two treatment groups. With both treatments, efficacy measures improved from baseline to each subsequent visit. Patients who received enteric-coated fenoprofen experienced the same im-

**Table 4**  
**Adverse Events Resulting in Withdrawal from the Study in 13 Patients Receiving Enteric-Coated Fenoprofen or Standard Fenoprofen Calcium for Treatment of Large-Joint Osteoarthritis**

Patient Number	Adverse Event	Days on Study Drug Before Treatment Was Discontinued
<i>Enteric-Coated Fenoprofen</i>		
1	Nausea	56
2	Moderate epigastric pain	27
3	Moderate epigastric pain, nausea	10
4	Moderate diarrhea	29
5	Blurred vision	52
<i>Standard Fenoprofen Calcium</i>		
1	Moderate nausea, vomiting, severe headache	1
2	Moderate dyspepsia	56
3	Allergic reaction/facial edema	98
4	Mild myocardial infarction	65
5	Severe urinary tract infection	49
6	Mild diarrhea	74
7	Moderate diarrhea	54
8	Cardiovascular accident	24

provement as those who received standard fenoprofen calcium. This improvement was the same for both the primary analysis, which compared baseline and endpoint variables, and for the secondary analysis, which compared variables at each of the three months of the treatment phase.

The only statistically significant differences occurred during the second month of the secondary analysis when all data were evaluated. At month 2, patients receiving fenoprofen calcium showed statistically significant greater improvement than patients receiving enteric-coated fenoprofen in the efficacy measures of pain with weight-bearing activity and pain on passive motion. However, this treatment difference was not significant at months 1 or 3. Furthermore, when the same analysis was performed on evaluable data only, no statistically significant difference was evident at any of the three months.

The adverse events encountered in this study did not have a statistically significant difference between the two treatment

groups and were of a type, severity, and incidence normally seen with fenoprofen and other NSAIDs (13). No deaths occurred during the study, and no permanently disabling adverse experiences were attributable to treatment with either formulation of fenoprofen. Only 13 (11.4%) patients withdrew from the study because of adverse events, and these patients were evenly distributed between the two treatment groups (eight in the standard fenoprofen group versus five in the enteric-coated group). Furthermore, most adverse events were minor and mild to moderately severe.

The number of patients completing the study was similar for the two treatment groups (80% in the enteric-coated fenoprofen group and 81% in the standard fenoprofen calcium group) and not unexpected for a three-month clinical study in outpatients.

This double-blind, randomized, parallel study provides evidence that enteric-coated fenoprofen is as effective as standard fenoprofen calcium for the treatment of large-joint osteoarthritis with a similar safety profile. Since enteric-coated fenoprofen reduces the risk of GI microbleeding (12), it may offer an additional safety factor for patients who require long-term administration of NSAIDs for large-joint osteoarthritis.

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