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A Randomized, Double-Blind, Crossover Clinical Trial of Diclofenac Plus Misoprostol Versus Acetaminophen in Patients With Osteoarthritis of the Hip or Knee

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Objective. **To perform a randomized, double-blind, crossover clinical trial of diclofenac + misoprostol versus acetaminophen in ambulatory patients with osteoarthritis of the hip or knee.**

Methods. **Patients in 12 ambulatory care settings were eligible if they were age >40 years and if they had Kellgren/Lawrence radiographic grade 2–4 osteoarthritis of the knee or hip and a score of ≥30 mm on a 100-mm visual analog pain scale. Patients were randomized to one of two groups, 75 mg diclofenac + 200 μg misoprostol twice daily or 1,000 mg acetaminophen 4 times daily (each for 6 weeks), and were then crossed over to the other treatment for 6 weeks. A placebo was included in each treatment regimen to enable double blinding. The primary outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index and the visual analog pain scale of the Multidimensional Health Assessment Questionnaire. Safety was assessed using a standard form to review adverse events.**

Results. **We enrolled 227 patients, of whom 218 provided data for the first treatment period and 181 provided data for both treatment periods. Significantly higher levels of improvement in the primary outcomes were seen for diclofenac + misoprostol than for acetaminophen ($P < 0.001$). Adverse events were more common when patients took diclofenac + misoprostol ($P = 0.046$). Diclofenac + misoprostol was rated as "better" or "much better" by 57% of the 174 patients who provided such ratings for both treatment periods, while acetaminophen was rated as "better" or "much better" by 20% of these patients, and 22% reported no difference ($P < 0.001$). Differences favoring diclofenac + misoprostol over acetaminophen were greater in patients with more severe osteoarthritis according to baseline pain scores, radiographs, or number of involved joints.**

Conclusion. **Patients with osteoarthritis of the hip or knee had significantly greater improvements in pain scores over 6 weeks with diclofenac + misoprostol than with acetaminophen, although patients with mild osteoarthritis had similar improvements with both drugs. Acetaminophen was associated with fewer adverse events.**

Osteoarthritis of the hip or knee is a major cause of medical disability and costs in the United States (1,2). The traditional standard drug therapy for osteoarthritis

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until the 1990s, nonsteroidal antiinflammatory drugs (NSAIDs), is associated with considerable gastrointestinal (GI) morbidity and excess mortality over long periods (3,4). Acetaminophen is associated with greater long-term safety than NSAIDs (3–6), and the American College of Rheumatology has recommended that acetaminophen be the initial drug therapy for osteoarthritis of the hip or knee (7–9).

Relatively little data are available concerning the efficacy of acetaminophen in osteoarthritis. One placebo-controlled clinical trial with 25 patients indicated that acetaminophen was superior to placebo (10). Two more recent randomized, controlled, clinical trials suggested that ibuprofen and naproxen did not differ significantly from acetaminophen (11,12), although most clinical measures were more favorable for NSAIDs than for acetaminophen. In two clinical surveys of 1,799 (13) and 300 (14) patients, 80% of patients who expressed a preference named an NSAID as "preferred" to acetaminophen or as the "best drug" for osteoarthritis, and a meta-analysis suggested that patients with osteoarthritis who were treated with NSAIDs had more pain relief than patients treated with acetaminophen (15).

These considerations led us to conduct an investigator-initiated, randomized, double-blind, crossover clinical trial of diclofenac + misoprostol (Arthrotec) compared to acetaminophen (the ACTA trial) in patients with osteoarthritis of the hip or knee. The methodology involved only questionnaires completed by patients and investigators at each of 5 visits and sent by facsimile to a university data center, a cost-effective design that could facilitate larger or less-expensive clinical trials for patients with osteoarthritis or other rheumatic diseases.

PATIENTS AND METHODS

Clinical trial protocol. Patients with osteoarthritis of the hip or knee were invited to participate in a randomized, double-blind, crossover clinical trial to compare results of treatment over 6 weeks with 75 mg diclofenac + 200 μg misoprostol (twice daily for a total daily dose of 150 mg diclofenac and 400 μg misoprostol) versus two 500-mg acetaminophen tablets (4 times daily for a total daily dose of 4,000 mg). The major inclusion criteria were age >40 years, Kellgren/Lawrence radiographic grade 2–4 osteoarthritis of the hip or knee (16), and a visual analog pain scale (17–19) score of ≥30 mm (range 0–100 mm). Exclusion criteria were restricted to severe comorbidities and hypersensitivity to acetaminophen, diclofenac, or misoprostol.

The protocol was written entirely by the principal investigator (TP), with suggestions from the other investigators (particularly GL). It was submitted to the sponsor for review, but no changes were requested. Funding was provided to the principal investigator, who then disbursed funds to investigators for enrolling patients and completing the protocol, as well as to statistical consultants. The sponsor provided funds and drugs, labeled the randomized drug, and had the only copy of the randomization code. The study was reviewed and approved by the Food and Drug Administration and was approved by the Institutional Review Board for the Protection of Human Subjects at Vanderbilt University and by the other 11 individual study sites.

The study was motivated by two conceptual hypotheses. The first hypothesis was that some patients would report greater pain relief with diclofenac + misoprostol versus acetaminophen, and vice versa. The second hypothesis was that in a large cohort, the extent of greater pain relief would be statistically more evident for diclofenac + misoprostol versus acetaminophen. The two primary outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (20,21), directed to the primary involved joint indicated by the patient, and the visual analog pain scale of the Multidimensional Health Assessment Questionnaire (MDHAQ) (19).

The study was conducted using only questionnaires completed by patients and health professionals to assess clinical status. All patient and physician questionnaires were completed at the study site and sent by facsimile to a data center within 24 hours. No site visits or exchanges of data by other means were conducted. The data center reviewed questionnaires for completeness within 24 hours and telephoned the clinical site to complete or clarify missing or unclear data.

At the study site at each of 5 visits, patients completed a standard 8-page questionnaire consisting of 5 parts. The first part was the WOMAC, which includes 3 sections of 100-mm (10-cm) visual analog scales (5 for pain, 2 for stiffness, and 17 for functional status) and is the standard for assessment and monitoring of osteoarthritis (22–25). A second WOMAC was used to assess specific response for a target most-involved joint (24,25), as has been suggested for osteoarthritis clinical trials, in contrast to the generalized WOMAC response. Third, the MDHAQ was used to assess functional status in activities of daily living (ADL) (18,26); it includes visual analog scales to assess pain, fatigue, GI distress, and global status. Fourth, the questionnaire included the Short Form 36 health survey (SF-36), a widely used generic (rather than "disease-specific") patient self-report questionnaire with 8 scales (for physical function, physical role, bodily pain, mental health, emotional role, social function, vitality, and general health perceptions) (27,28). Finally, short questionnaires unique to each visit were developed for completion by the patient and health professional. These included queries concerning clinical status, intercurrent illnesses, general medical information, and adverse events.

In treatment period 1, group I patients received 75 mg diclofenac + 200 μg misoprostol (to be taken twice daily) and acetaminophen placebo (2 pills to be taken 4 times daily). In period 2, these patients received 500-mg acetaminophen tablets (2 pills to be taken 4 times daily) and diclofenac + misoprostol placebo (to be taken twice daily). Group II patients received these drugs in the opposite sequence for the two treatment periods. Active drug and placebo pills had identical appearances. Patients were randomized to the two treatment groups in blocks of 4 patients each (2 to each group) and provided with 45-day supplies of drug and placebo in bottles labeled with a randomization number. Allocation of

patients was concealed from personnel at the study sites and data center.

The protocol included 5 study visits. Visit 1 was a screening visit. Eligible volunteer patients were asked to take no medications for osteoarthritis (other than propoxyphene as a rescue medication) for a 3–7-day washout period prior to visit 2, at which time the patient was randomly assigned to group I or group II, given a 45-day supply of the first drug and placebo, and asked to return 6 weeks later. Visit 3 occurred 6 weeks later to assess responses to the first drug. Patients were given the option of continuing to the second treatment period. Those who volunteered were asked to comply with a second 3–7-day washout period (5 times the half-life of either drug) prior to visit 4, at which time a 45-day supply of the second drug and placebo was provided. Visit 5 occurred 6 weeks later to assess final clinical status, possible protocol violations, adverse events, and patient and health professional preferences for the first versus the second treatment.

Patients were given an extra standard questionnaire, to be completed in the event they chose to discontinue treatment early (before visit 5 at day 42) due to lack of benefit, adverse events, or any other reason. Patients were asked to complete this questionnaire on the day they discontinued treatment to monitor their status if a visit to the study site could not be arranged for that day. If withdrawal from the study occurred during period 1, the patient was given the option of enrolling in period 2 (3–7 days after discontinuing the first treatment).

Statistical methods. The data were entered into a database using MEDLOG software (Incline Village, NV) and transferred to PC SAS (Sas Institute, Cary, NC) for further analyses. For both group I (diclofenac + misoprostol followed by acetaminophen) and group II (acetaminophen followed by diclofenac + misoprostol), means and their corresponding SEM were computed to describe the distributions of demographic, clinical, and patient questionnaire response variables from the WOMAC, MDHAQ, and SF-36 scales, as well as distributions of investigator estimates of patient status at the screening visit (visit 1). Means and SEM were also used in computing the baseline distributions of the corresponding variables at the beginning of each treatment period, as well as distributions of the corresponding changes from baseline for each treatment period.

Distributions of categorical demographic variables were described for each group with frequencies and/or percentages. Such descriptions were also provided for treatment-emergent adverse events for each treatment and for the patient and physician ratings of the better therapy (i.e., diclofenac + misoprostol better, no difference, acetaminophen better). The extent of random imbalances in comparisons of the two groups at screening (visit 1) was described with *P* values according to chi-square tests for dichotomous demographic variables and Wilcoxon rank sum tests for all other variables.

The primary method for comparing the effects of diclofenac + misoprostol with those of acetaminophen for all of the response variables was analysis of covariance for the change during period 1 (i.e., visit 3 − visit 2). In these analyses, the corresponding screening (visit 1) and baseline (visit 2) values were the covariables. There were two types of major supportive analyses: one applied analysis of covariance to changes during period 2 (i.e., visit 5 − visit 4), with the corresponding values at visits 1, 2, and 4 as the covariables; the other applied repeated-measures analysis of covariance to the changes during both periods through generalized estimating equations (29).

The method for both periods provided a comprehensive analysis through a statistical model with components for period, treatment, visit 1, visit 2, and baseline, and with management of patients as a random sampling unit. This method was also used to evaluate similarity of treatment effects for the two periods through an expanded model that included treatment × period interaction (or carryover effects) as an additional component. It is of additional interest that comparisons for visit 4 (with visits 1 and 2 as the covariables) supported similarity of the two groups at the beginning of period 2. Such similarity strengthened the usefulness and interpretability of the data at visit 5 for period 2, particularly since 45 patients (19 in group I and 26 in group II) withdrew from the study prior to visit 5.

The principal analyses addressed the two primary outcome measures (WOMAC for the primary involved joint and MDHAQ pain scale for the 218 patients [106 in group I and 112 in group II] for whom there were data for visit 3 − visit 2) without any formal adjustment for multiple comparisons, since the *P* values for both were less than 0.011 and so were significant at the 2-sided 0.05 level by the Bonferroni method or any of its extensions (30). Similar results were seen with the conservative assumptions of 0 change for the 8 patients with no data after visit 2 and the same change for visit 3 − visit 2 as was seen for visit 5 − visit 4 for the 1 patient missing visit 3 and with data for visits 4 and 5; therefore, missing data for 9 patients at visit 3 (6 in group I and 3 in group II) was not an issue for the primary analyses. The results from analyses for period 2 and for both periods were also robust to such methods for managing missing data at visit 5, and the *P* values from the primary analyses for period 1 and their supportive counterparts for period 2 were confirmed with analogous nonparametric methods (31).

Differences in patient ratings over 6 weeks of either diclofenac + misoprostol or acetaminophen, from before treatment to after treatment, were compared according to the severity of osteoarthritis in individual patients using the screening values of 4 indicators: 1) the total WOMAC score for the target joint, 2) the MDHAQ visual analog pain scale, 3) the maximum Kellgren/Lawrence radiographic grade in either knee or hip, and 4) the patients' classification of joint pain as involving only one knee, only both knees, or one or both hips with or without one or both knees. A pooled severity index (32) was also evaluated based on 4 indicators of milder osteoarthritis: lowest tertile at screening for the target WOMAC total score, lowest tertile at screening for the MDHAQ visual analog pain scale, Kellgren/Lawrence grade 2, and pain in only one knee. The pooled severity index has a value of 0 (for mild osteoarthritis) if 3 or 4 of the indicators apply to a patient, 1 if 2 of the indicators apply to a patient, 2 if only 1 of the indicators applies to a patient, and 3 (for severe osteoarthritis) if none of the indicators applies to a patient. The analyses concerning the indicators of severity and pooled severity index were applied by expanding the repeated-measures analysis of covariance for the data from both periods to include the corresponding indicator or pooled severity index and its interaction with treatment.

The prevalence of adverse events was compared for the two treatments by an extension of the McNemar test (33). The *P* values using this method were based on a weighted combi-

Table 1. Demographic, disease, and patient questionnaire measures at screening in two groups of patients randomized to receive diclofenac + misoprostol or acetaminophen first in a crossover trial*

Variable	Group I (n = 112)	Group II (n = 115)	*P*
Demographic measures			
Age, years	62 ± 1.30	61 ± 1.24	0.828
Female, %	70	71	0.884
Married, %	58	56	0.789
Caucasian, %	88	89	0.839
Working full time, %	23	25	0.758
Retired or disabled, %	46	44	0.791
≤12 years of education, %	41	50	0.231
Osteoarthritis measures at screening			
Kellgren/Lawrence radiographic grade of osteoarthritis (1–4)	2.8 ± 0.070	2.9 ± 0.077	0.323
Severity of joint space narrowing (0–3)	1.8 ± 0.089	1.9 ± 0.097	0.284
Severity of osteophytes (0–3)	1.5 ± 0.081	1.7 ± 0.087	0.083
Global severity of osteoarthritis (0–3)	1.8 ± 0.070	1.8 ± 0.068	0.740
Primary outcome measures			
WOMAC target joint (0–100)	40.2 ± 1.94	42.1 ± 2.07	0.378
MDHAQ visual analog pain scale (0–100)	52.9 ± 1.90	52.5 ± 1.92	0.851
Other measures			
SF-36 bodily pain (0–100)	36.7 ± 0.59	35.2 ± 0.68	0.033
MDHAQ basic ADL (0–3)	1.45 ± 0.033	1.47 ± 0.034	0.634
MDHAQ GI distress (0–100)	17.9 ± 2.28	19.0 ± 2.24	0.644
MDHAQ global patient status (0–100)	27.7 ± 2.00	30.4 ± 2.09	0.418
Investigator estimate of patient global status (0–100)	39.3 ± 1.65	42.3 ± 1.72	0.214

* Except where otherwise indicated, values are the mean ± SEM. Group I received diclofenac + misoprostol first (period 1), followed by acetaminophen (period 2). Group II received acetaminophen first (period 1), followed by diclofenac + misoprostol (period 2). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; MDHAQ = Multidimensional Health Assessment Questionnaire; SF-36 = Short Form 36 health survey; ADL = activities of daily living; GI = gastrointestinal.

nation of the difference between event rates for patients receiving both treatments and its counterpart for patients receiving only one of the treatments; the weights were reciprocals of the corresponding variances.

RESULTS

Patients. Overall, 227 patients were randomized at the 12 sites (mean 19 patients/site); 112 were ran-

Table 2. Baseline values and changes after 6 weeks of treatment in WOMAC score, MDHAQ visual analog pain scale score, and other measures of patient status at the end of each treatment period in the crossover trial*

	Group I				Group II			
	Period 1 (diclofenac + misoprostol)		Period 2 (acetaminophen)		Period 1 (acetaminophen)		Period 2 (diclofenac + misoprostol)	
Variable†	Baseline	Change at 6 weeks	Baseline	Change at 6 weeks	Baseline	Change at 6 weeks	Baseline	Change at 6 weeks
Primary outcome measures								
WOMAC target joint	42.5 ± 2.1	−12.2 ± 2.0	37.4 ± 2.5	−2.1 ± 1.9	44.8 ± 2.1	−6.6 ± 1.7	40.5 ± 2.6	−12.9 ± 2.1
MDHAQ visual analog pain scale	53.7 ± 1.7	−20.8 ± 2.5	45.3 ± 2.8	−0.4 ± 2.6	58.8 ± 1.9	−13.1 ± 2.7	53.3 ± 2.9	−24.6 ± 2.8
Other measures								
SF-36 bodily pain	36.4 ± 0.7	5.3 ± 0.8	38.0 ± 0.9	0.6 ± 0.8	35.2 ± 0.7	2.3 ± 0.8	36.5 ± 0.9	5.7 ± 0.9
MDHAQ basic ADL	0.52 ± 0.04	−0.16 ± 0.03	0.52 ± 0.04	−0.04 ± 0.03	0.55 ± 0.04	−0.08 ± 0.03	0.52 ± 0.04	−0.18 ± 0.04
MDHAQ Gl distress	18.2 ± 2.2	10.9 ± 3.0	24.4 ± 2.9	−4.4 ± 2.5	21.5 ± 2.0	4.9 ± 2.6	23.1 ± 2.7	4.9 ± 3.2
MDHAQ global patient status	32.8 ± 2.2	−6.7 ± 2.3	31.1 ± 2.3	2.7 ± 2.4	35.6 ± 2.2	−3.9 ± 2.4	37.3 ± 2.7	−12.5 ± 2.6
Investigator estimate of patient global status	44.8 ± 1.8	−9.3 ± 1.8	47.5 ± 2.0	−0.8 ± 1.9	46.9 ± 1.8	−3.6 ± 1.8	45.3 ± 2.0	−10.3 ± 2.2
Investigator estimate of change in status	56.1 ± 1.3	−18.4 ± 2.2	56.7 ± 1.9	−4.4 ± 2.2	57.0 ± 1.5	−12.1 ± 2.2	54.2 ± 1.8	−20.5 ± 2.5

* Values are the mean ± SEM. See Table 1 for definitions and explanations.
† All variables were reported on a 100-mm visual analog scale, except for MDHAQ basic ADL, which was reported on a rating scale of 0–3.

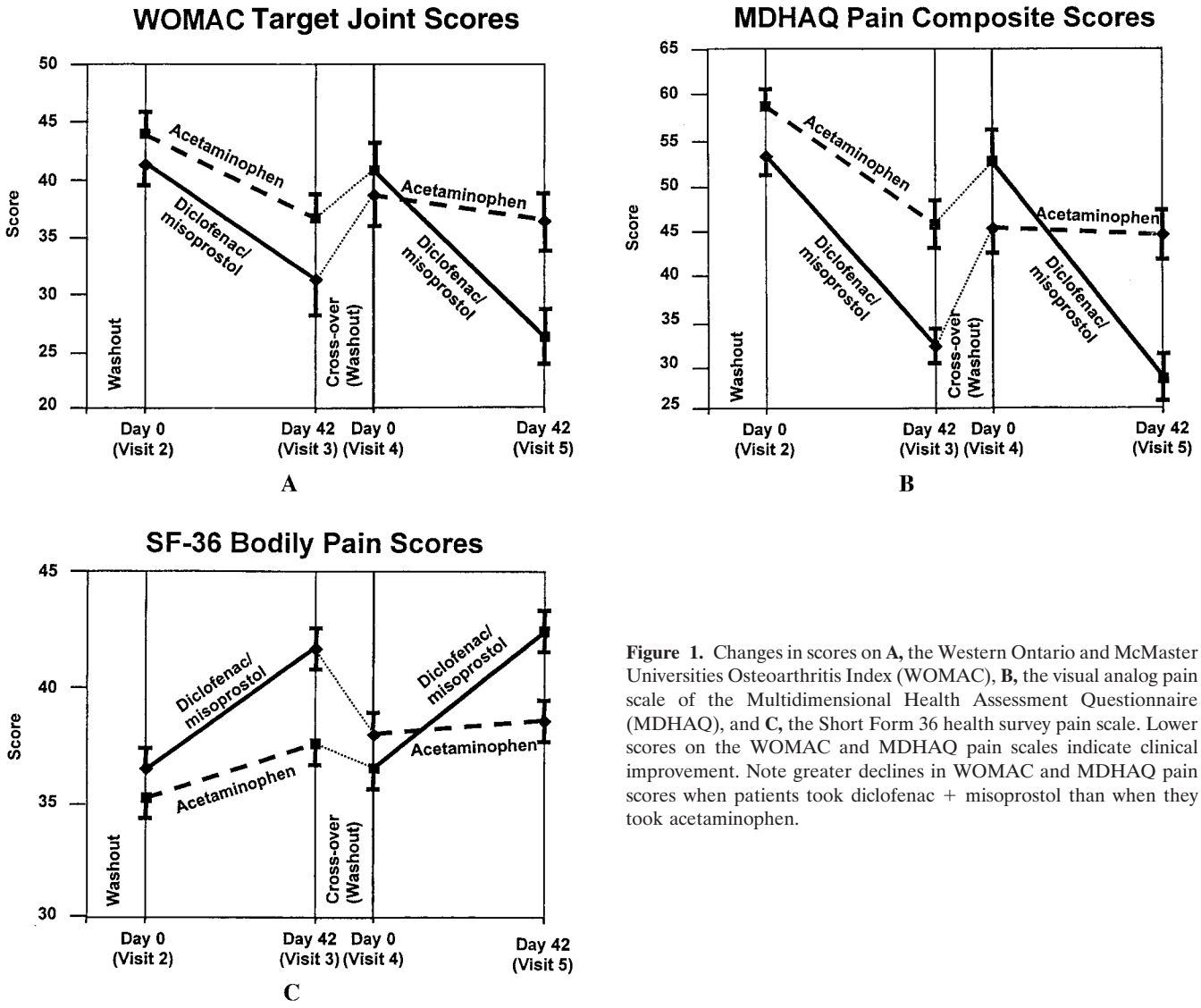

Figure 1. Changes in scores on **A,** the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), **B,** the visual analog pain scale of the Multidimensional Health Assessment Questionnaire (MDHAQ), and **C,** the Short Form 36 health survey pain scale. Lower scores on the WOMAC and MDHAQ pain scales indicate clinical improvement. Note greater declines in WOMAC and MDHAQ pain scores when patients took diclofenac + misoprostol than when they took acetaminophen.

domly assigned to group I and 115 to group II. Patients who were randomized to group I or group II were similar in demographic measures of age, sex, marital status, and formal education level; in osteoarthritis measures of radiographic grade, severity of joint space narrowing and osteophytes, and mean global severity of osteoarthritis at the time of screening; and (other than for SF-36 bodily pain, which is likely explained by multiple comparisons) in measures to assess clinical status from the WOMAC, MDHAQ, and SF-36 questionnaires at screening (Table 1). The primary joint involved by osteoarthritis was identified as the hip by 22% of patients and as the knee by 78%. No significant differences at baseline were seen according to the site at which the patient was studied.

Comparisons of results of treatment with diclofenac + misoprostol and acetaminophen. During the first 6-week treatment period, scores for the WOMAC scale in the most-involved joint fell by 12.2 units from a mean of 42.5 units in group I patients who took diclofenac + misoprostol, and by 6.6 units from a mean of 44.8 units in patients who took acetaminophen (Table 2 and Figure 1A). The covariance-adjusted difference of 6.39 units between the means for the two treatments was statistically significant (2-sided $P = 0.011$) (Table 3). In the second 6-week treatment period, mean WOMAC scale scores fell by 2.1 units in group I patients who were then taking acetaminophen, compared with a decrease of 12.9 units in patients who were then taking diclofenac + misoprostol (Table 2 and Figure 1A). The correspond-

Table 3. Estimated differences between diclofenac + misoprostol and acetaminophen during period 1 and period 2 and during both periods*

Variable†	Period 1‡ Estimate ± SEM	Period 1‡ *P*	Period 2§ Estimate ± SEM	Period 2§ *P*	Both periods¶ Estimate ± SEM	Both periods¶ *P*	Treatment × period *P*#
Primary outcome measures							
WOMAC target joint	−6.39 ± 2.49	0.011	−9.53 ± 2.41	0.001	−7.75 ± 1.81	<0.001	0.303
MDHAQ visual analog pain scale	−11.1 ± 3.5	0.002	−19.9 ± 3.3	<0.001	−14.6 ± 2.3	<0.001	0.072
Other measures							
SF-36 bodily pain	3.40 ± 1.06	0.002	4.12 ± 1.03	<0.001	3.83 ± 0.75	<0.001	0.589
MDHAQ basic ADL	−0.08 ± 0.04	0.030	−0.15 ± 0.04	<0.001	−0.11 ± 0.02	<0.001	0.251
MDHAQ GI distress	3.7 ± 3.6	0.307	7.7 ± 3.2	0.018	5.5 ± 2.2	0.013	0.529
MDHAQ global patient status	−4.1 ± 2.9	0.156	−11.8 ± 3.2	<0.001	−7.4 ± 2.0	<0.001	0.094
Investigator estimate of patient global status	−6.5 ± 2.3	0.005	−10.2 ± 2.5	<0.001	−8.2 ± 1.6	<0.001	0.273
Investigator estimate of change in status	−6.8 ± 3.0	0.026	−16.4 ± 3.2	<0.001	−11.2 ± 2.2	<0.001	0.021

* See Table 1 for definitions and explanations. See Patients and Methods for description of visits.
† All variables were reported on a 100-mm visual analog scale, except for MDHAQ basic ADL, which was reported on a rating scale of 0–3.
‡ Results from analysis of covariance are shown for visit 3 − visit 2, with visits 1 and 2 as covariables.
§ Results from analysis of covariance are shown for visit 5 − visit 4, with visits 1, 2, and 4 as covariables.
¶ Results from repeated-measures analysis of covariance are shown for the combined data for visit 3 − visit 2 and visit 5 − visit 4. The model included components for period, treatment, visit 1, visit 2, and baseline
# From repeated-measures analysis of covariance with the model described in footnote ¶ expanded to include treatment × period interaction (or carryover effects).

ing covariance-adjusted difference of 9.53 units was also significant (2-sided $P < 0.01$) (Table 3). The estimated difference for both periods was 7.75 units ($P < 0.001$) (Table 3).

The mean MDHAQ visual analog pain scores in period 1 fell by 20.8 units in patients who took diclofenac + misoprostol, compared with a decrease of 13.1 units in patients who took acetaminophen (Table 2 and Figure 1B). In period 2, mean MDHAQ visual analog pain scale scores fell by 0.4 units in patients who took acetaminophen and by 24.6 units in patients who took diclofenac + misoprostol (Table 2 and Figure 1B). The corresponding covariance-adjusted differences between the means for the two treatments were 11.1 units for period 1, 19.9 units for period 2, and 14.6 units for both periods, all of which were statistically significant (2-sided $P < 0.01$) (Table 3).

In addition to the significant differences between treatments for scores according to the two primary outcomes noted above, many other scale scores were significantly more improved when patients took diclofenac + misoprostol rather than acetaminophen, including mean SF-36 pain scores (a higher SF-36 score indicates better status, unlike higher WOMAC and MDHAQ scores, which indicate poorer status), MDHAQ scores for basic ADL, and global health ($P < 0.001$ for both periods) (Tables 2 and 3). This was also true for mean WOMAC subscale scores for pain, stiffness, and function, as well as for SF-36 scores for physical function (data not shown). Similar findings were seen for investigators' estimates of patient global status and change in status over 6 weeks ($P < 0.001$ for both periods) (Tables 2 and 3). However, the MDHAQ GI distress scale score was higher in both periods when patients took diclofenac + misoprostol than when patients took acetaminophen.

The change in scores over the 6 weeks during which patients took diclofenac + misoprostol did not differ significantly whether this drug was the first or second treatment in the crossover design. Although differences in scores when acetaminophen was taken as the first drug appeared better than when it was taken as the second drug, carryover effects (or treatment × period interaction) were reasonably compatible with what might be expected by chance, with only 1 of the *P* values below 0.05 and only 3 below 0.10 (Table 3).

Analyses of treatment differences according to severity of osteoarthritis. Differences between results after diclofenac + misoprostol versus acetaminophen were more marked in patients with greater disease severity (Table 4). Changes in patient ratings according to the two primary outcome measures, the WOMAC and the MDHAQ pain scale, were similar in patients with the mildest osteoarthritis according to 4 indicators: the screening values for each of the 2 primary outcome measures, the maximum Kellgren/Lawrence radiographic grade in either knee or hip, and the patient classification of joint pain as involving only one knee,

Table 4. Estimated differences between diclofenac + misoprostol and acetaminophen for both periods for subgroups corresponding to several criteria for severity of osteoarthritis*

Criterion for severity, subgroup	Target WOMAC total score†			MDHAQ pain VAS†		
	n	Estimate ± SEM	*P*	n	Estimate ± SEM	*P*
Screening value‡						
First tertile	76	−3.14 ± 3.01	0.296	77	−4.89 ± 4.25	0.250
Second tertile	75	−9.47 ± 2.79	0.001	73	−16.59 ± 3.17	<0.001
Third tertile	76	−12.19 ± 3.65	0.001	77	−20.96 ± 4.39	<0.001
Kellgren/Lawrence grade (highest for 2 knees and 2 hips)						
2	71	−3.03 ± 3.10	0.327	71	−12.90 ± 4.19	0.002
3	91	−9.88 ± 2.87	0.001	91	−12.19 ± 3.90	0.002
4	47	−14.97 ± 3.41	<0.001	47	−21.81 ± 4.62	<0.001
Patient joint classification for pain						
1 knee only	33	1.04 ± 3.51	0.766	33	−2.43 ± 4.45	0.586
2 knees only	57	−12.66 ± 3.55	<0.001	57	−14.81 ± 4.38	0.001
Other	133	−7.52 ± 2.44	0.002	133	−16.24 ± 3.23	<0.001
Pooled severity index, value§						
0	26	0.78 ± 4.36	0.858	26	−0.87 ± 5.53	0.875
1	50	−1.45 ± 3.82	0.704	50	−8.84 ± 5.51	0.109
2	74	−6.72 ± 3.61	0.063	74	−14.02 ± 4.58	0.002
3	77	−14.70 ± 2.83	<0.001	77	−22.05 ± 3.63	<0.001

* See Table 1 for definitions and explanations. See Patients and Methods for description of visits.
† Results for repeated-measures analysis of covariance are shown for the combined data for visit 3 − visit 2 and visit 5 − visit 4. The model included components for period, treatment, visit 1, visit 2, and baseline.
‡ For the target WOMAC total score, the first tertile is <30.46, the second tertile is 30.46–49.63, and the third tertile is >49.63. For the MDHAQ pain visual analog scale (VAS), the first tertile is <44.00, the second tertile is 44.00–63.00, and the third tertile is >63.00.
§ The pooled severity index is based on 4 indicators of milder osteoarthritis: joint pain in only one knee, Kellgren/Lawrence grade 2, lowest tertile at screening for the target WOMAC total score, and lowest tertile at screening for the MDHAQ pain VAS. It has a value of 0 (for mild osteoarthritis) if 3 or 4 of the indicators apply to a patient, 1 if 2 of the indicators apply to a patient, 2 if only 1 of the indicators applies to a patient, and 3 (for severe osteoarthritis) if none of the indicators applies to a patient.

Table 5. Treatment-emergent adverse events reported during 6 weeks of diclofenac + misoprostol or acetaminophen in the crossover trial*

	Diclofenac + misoprostol	Acetaminophen	*P*†
No. of patients exposed to drug	203	210	–
No. of patients not dropping out early	195	205	–
Any event	105 (53.8)	94 (45.9)	0.046
Serious events			
Myocardial infarction	2 (1.0)	1 (0.5)	–
Hemorrhagic diarrhea	1 (0.5)	0 (0)	–
Acute abdomen	1 (0.5)	0 (0)	–
Other events‡			
Any GI event	67 (34.4)	50 (24.4)	0.006
Diarrhea	39 (20.0)	29 (14.1)	0.072
Dyspepsia	19 (9.7)	16 (7.8)	0.532
Nausea and/or vomiting	15 (7.7)	8 (3.9)	0.091
Abdominal pain	13 (6.7)	4 (2.0)	0.001
Constipation	3 (1.5)	3 (1.5)	0.662
Headache	5 (2.6)	7 (3.4)	0.538
SGOT level 1–<1.5× normal	15 (7.7)	9 (4.4)	–
SGOT level 1.5–3× normal	6 (3.1)	1 (0.5)	–
SGOT level >3× normal (3.125× normal)	1 (0.5)	0 (0)	–
Total with abnormal SGOT level	22 (11.3)	10 (4.9)	0.009

* Except where otherwise indicated, values are the number (%) of patients. GI = gastrointestinal; SGOT = serum glutamic oxaloacetic transaminase.
† From extended McNemar test.
‡ No other event occurred in >5% of patients exposed to either drug.

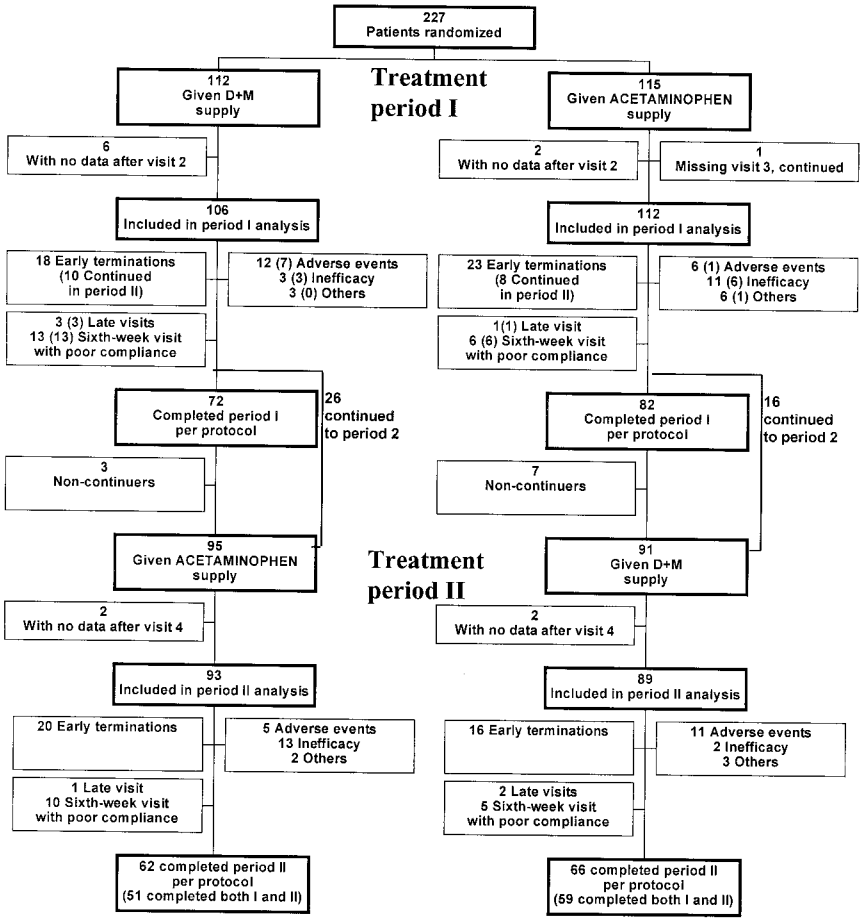

Figure 2. Classification of dispositions of all 227 patients who were randomized in the crossover clinical trial. Group I includes 112 patients assigned to diclofenac + misoprostol (D+M) in treatment period 1 and acetaminophen in treatment period 2. Group II includes 115 patients assigned to acetaminophen in treatment period 1 and D+M in treatment period 2. Boxes at left in each group show numbers of noncontinuing patients, patients with early terminations as well as those with late visits, and patients with poor compliance (who returned more pills than expected). Boxes at right in each group provide reasons for early terminations. Numbers in parentheses indicate patients who continued to treatment period 2. See Patients and Methods for description of treatment periods and visits.

only both knees, or one or both hips with or without one or both knees (Table 4). A pooled severity index for a combination of these indicators yielded the same results (Table 4). Further analyses of these data indicated statistically significant ($P < 0.05$) interactions for each of the 4 severity indicators and the pooled severity index for the WOMAC, and for all severity indicators (except the Kellgren/Lawrence grade) and the pooled severity index for the MDHAQ pain scale (data not shown).

Adverse events. Some adverse event was reported by 54% of the 195 patients who took diclofenac + misoprostol, compared with 46% of the 205 patients who took acetaminophen ($P = 0.046$) (Table 5). Five adverse events were regarded as serious. Four occurred in patients taking diclofenac + misoprostol, including 2 myocardial infarctions, 1 episode of hemorrhagic diarrhea, and 1 episode of acute abdomen. One myocardial infarction occurred in a patient taking acetaminophen. The patient with hemorrhagic diarrhea was an 83-year-old woman who experienced diarrhea and stomach cramps 1 week after starting the second treatment period with diclofenac + misoprostol. Colonoscopy indicated marked left-sided diverticulosis with a few erosions thought likely to be secondary to diclofenac use.

Table 6. Basis for withdrawal of patients who did not complete both arms of the crossover clinical trial*

	Group I			Group II		
	Period 1 baseline only†	Period 1 baseline and review‡	Period 2 baseline only§	Period 1 baseline only†	Period 1 baseline and review‡	Period 2 baseline only§
Adverse events						
GI discomfort		2			2	
Diarrhea		3			4	
Acute abdomen	1					
Elevated liver enzyme levels					1	
Myocardial infarction	1					
Headache		1			1	
Other reasons						
Lack of benefit	1	1			7	
Administrative	2	1		1	3	2
Noncompliance	1	3	2	1	4	
Total	6	11	2	2	22	2

* Values are the number of patients. GI = gastrointestinal. See Table 1 for explanations.
† These patients provided baseline data only for period 1.
‡ These patients provided baseline and followup data for period 1 but no data for period 2.
§ These patients provided baseline and followup data for period 1 and baseline data for period 2.

The patient with an acute abdomen was a 79-year-old woman who was admitted to the hospital because of severe abdominal pain 5 weeks after starting the first treatment period with diclofenac + misoprostol. The patient had a history of abdominal pain related to postsurgical adhesions. A small bowel obstruction was found, and surgery for lysis of adhesions was performed. All patients with serious adverse events recovered.

Nonserious adverse GI events were more common for patients taking diclofenac + misoprostol than for those taking acetaminophen. These included any GI event (34% versus 24%, respectively; $P = 0.006$), diarrhea (20% versus 14%; $P = 0.072$), dyspepsia (10% versus 8%; $P = 0.532$), nausea or vomiting (8% versus 4%; $P = 0.091$), and abdominal pain, (7% versus 2%; $P = 0.001$). Elevated levels of serum glutamic oxaloacetic transaminase occurred in 22 patients who took diclofenac + misoprostol (11%) and in 10 patients who took acetaminophen (5%) ($P = 0.009$). Most elevations were <1.5 times normal, and all levels returned to normal within 4 weeks of drug discontinuation. No hematologic adverse events were seen. As noted above, the MDHAQ GI distress scale score was increased, indicating a higher level of GI symptomatology, in patients who took diclofenac + misoprostol compared with those who took acetaminophen ($P = 0.013$ for both periods) (Tables 2 and 3).

Classification of dispositions of all 227 patients who were randomized (Figure 2) indicates that 112 patients were assigned to group I and 115 to group II. Nine patients did not provide data for period 1 response variables, including 8 patients who did not complete period 1, 6 of whom took diclofenac + misoprostol and 2 of whom took acetaminophen (Table 6). Thirty-three patients completed period 1 and chose not to continue to period 2 (11 who took diclofenac + misoprostol and 22 who took acetaminophen) (Table 6). Reasons cited for noncontinuation included GI discomfort or diarrhea (5 patients who took diclofenac + misoprostol and 6 who took acetaminophen) and lack of benefit (1 patient who took diclofenac + misoprostol and 7 who took acetaminophen). Four patients completed period 1 and began, but did not complete, period 2. Overall, data were available for both periods for 181 of the 227 patients (80%) who were randomized.

Overall ratings of the two drugs according to patient and physician. Patients were asked on their final visit to rate the drugs taken during the two treatment periods (Table 7). Diclofenac + misoprostol was reported as "better" or "much better" by 57% of the 174 patients who provided such ratings, while acetaminophen was reported to be "better" or "much better" by 20% of these patients, and 22% reported no difference between the two drugs ($P < 0.001$). Ratings of the status of 178 patients by health professionals were similar; diclofenac + misoprostol was rated "best" for 58% of patients, acetaminophen was rated "best" for 22%, and the drugs were rated as having "no difference" for 20% ($P < 0.001$) (Table 7).

Table 7. Patient and physician ratings of better therapy in crossover clinical trial of diclofenac + misoprostol versus acetaminophen*

	Group I	Group II	Total
Patient ratings			
Diclofenac + misoprostol better or much better	52 (58)	48 (57)	100 (57)
No difference	18 (20)	21 (25)	39 (22)
Acetaminophen better or much better	20 (22)	15 (18)	35 (20)
Physician ratings			
Diclofenac + misoprostol better	54 (59)	49 (56)	103 (58)
No difference	15 (16)	21 (24)	36 (20)
Acetaminophen better	22 (24)	17 (20)	39 (22)

* Values are the number (%) of patients. See Table 1 for explanations.

DISCUSSION

In this investigator-initiated, randomized, double-blind, crossover clinical trial, statistically significantly better changes were seen for scores on the WOMAC (20,21) and the MDHAQ visual analog pain scale (19) in patients during treatment with diclofenac + misoprostol than in those during treatment with acetaminophen. Also, except for the MDHAQ GI distress scale, significant differences were seen for diclofenac + misoprostol compared with acetaminophen on the subscales of the WOMAC, SF-36, and MDHAQ. Such significant differences were seen for the essentially intent-to-treat analysis of period 1, as though the study had a traditional parallel-groups design, and they were further reinforced in the crossover period 2. Moreover, similar findings were obtained for intent-to-treat analyses of all randomized patients (including the 9 patients with data for visit 2 but not for visit 3) through methods that replace missing data either with conservative values (to reduce treatment differences) or with regression-predicted values (Pinto C, Wang X, Koch G: unpublished observations).

More GI adverse events were reported by patients taking diclofenac + misoprostol than by those taking acetaminophen, as expected. Diarrhea, a recognized adverse event associated with the misoprostol component (34,35), was reported by 20% of patients taking diclofenac + misoprostol and by 14% of patients taking acetaminophen. Nausea and abdominal pain were also more frequent with diclofenac + misoprostol, but were not absent with acetaminophen. These observations are consistent with the finding that the only patient questionnaire scores reflecting poorer patient status while taking diclofenac + misoprostol versus acetaminophen were on the MDHAQ GI distress scale, a finding that also supports the face validity of this scale.

Acetaminophen has lower GI toxicity than NSAIDs, but evidence for the efficacy of acetaminophen in osteoarthritis is limited. One study of 25 patients in a crossover design indicated greater efficacy of acetaminophen versus placebo (10). Two clinical trials indicated comparable efficacy of ibuprofen or naproxen versus acetaminophen (11,12), although close inspection of the results in these studies indicates advantages of ibuprofen or naproxen that were not statistically significant, perhaps due to an insufficient number of patients (Type II error). A meta-analysis suggested that patients with osteoarthritis who were treated with NSAIDs had more pain relief than patients treated with acetaminophen (15), and two clinical surveys suggested patient preference for an NSAID over acetaminophen (13,14). In the study reported here and in another study (36), greater differences in efficacy of NSAIDs were seen in patients with more severe osteoarthritis.

Although statistically significant findings have emerged from this clinical trial, limitations to interpretation of the results are recognized. First, the data are short term over 6 weeks of therapy, and short-term data may not be directly applicable to long-term outcomes in rheumatic diseases (37,38). Second, all patients in this study came to the attention of rheumatologists. Although some patients who had never seen a rheumatologist were recruited through advertising, ~80% of the patients had seen a rheumatologist. It is possible that patients not seen by rheumatologists might respond differently to acetaminophen versus diclofenac + misoprostol or another NSAID, and it would be of interest to conduct a similar study in patients who had never seen a rheumatologist. Third, this was only a single trial, and further studies appear to be needed to assess the benefits of acetaminophen in the management of osteoarthritis of the hip or knee. Fourth, there was no placebo arm, and further comparisons with a placebo would appear to be of interest.

These observations illustrate potential advantages of a crossover design for studying the relative

performance of two drugs. It is sometimes difficult to interpret patient attributions of lack of benefit or toxicity, since a patient may continue a drug with moderate GI distress if there is considerable benefit, but may discontinue a drug because of "toxicity" if there is no perceived benefit. The crossover design allowed both patients and health professionals to identify a preferred treatment and also provided greater statistical power. Additional methodologic advances may be derived from the collection of all data using simple questionnaires (39–41) completed by health professionals and patients and sent by facsimile to a data center. This approach could provide an infrastructure for large, simple clinical trials (42) at relatively low costs compared with current approaches, allowing many more patients with rheumatic diseases to be assessed in clinical trials.

These data may suggest possible further reassessment of guidelines for using acetaminophen as initial drug therapy for osteoarthritis of the knee or hip (7–9). Those patients who report previous benefit with acetaminophen, have no experience with acetaminophen, have less severe osteoarthritis, or express a wish to avoid side effects might be given acetaminophen. However, patients who report previous lack of benefit using acetaminophen in reasonable doses might be treated with an NSAID instead. Selective cyclooxygenase 2–inhibiting antiinflammatory drugs (43,44) might be a suitable alternative to diclofenac + misoprostol in certain patients, particularly those who are at risk for GI problems associated with NSAIDs. Further clinical trials and long-term observations are needed to advance optimal therapy for people with osteoarthritis of the hip or knee.

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