Severity of Knee Pain Does Not Predict a Better Response to an Antiinflammatory Dose of Ibuprofen than to Analgesic Therapy in Patients with Osteoarthritis

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ABSTRACT. ***Objective.*** To determine whether greater pain intensity at initiation of treatment predicted better response to ibuprofen than to acetaminophen in subjects with knee osteoarthritis (OA).

Methods. Data from 182 patients with knee OA who had taken part in a 4 week randomized, double blind, parallel comparison of 4000 mg/day acetaminophen vs either 1200 or 2400 mg/day ibuprofen were reanalyzed using Pearson correlation coefficients for baseline pain severity, treatment assignment, and treatment response. Pain measures were visual analog scales for overall pain, resting pain, and walking pain. Baseline pain severity was divided into low, medium, and high tertiles, and treatment related differences in pain response were sought with pairwise t tests. Two-factor analysis of variance (ANOVA) models were used to seek interactions between baseline pain severity and treatment group, which would indicate differential drug treatment responsiveness.

Results. Greater baseline pain predicted greater pain relief with all 3 treatments. Patients with a high level of baseline rest pain appeared to respond better to ibuprofen 2400 mg/day than to the other treatments, but this difference was not evident after correction for multiple statistical tests. ANOVA did not reveal significant differences in response to the 3 treatments or a significant interaction.

Conclusion. Our data suggest that acetaminophen and ibuprofen are comparably effective in treating knee OA pain, even when the pain is severe. (J Rheumatol 2001;28:1073–6)

Key Indexing Terms:
OSTEOARTHRITIS KNEE PAIN TREATMENT

The American College of Rheumatology (ACR) Guidelines for the Medical Management of Osteoarthritis (OA)[1,2] are currently being reconsidered, at least partly because of the recent availability of cyclooxygenase 2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAID) and effective agents for prophylaxis of NSAID associated gastrointestinal ulcers[3]. Such guidelines are important insofar as they influence treatment options provided by managed care organizations, formulary committees, and practicing physicians. The 1995 Guidelines recommended an initial trial of acetaminophen (ACET) before resorting to an NSAID, largely because of the risk of inducing gastrointestinal ulcers, bleeding, and perforation with NSAID. NSAID of first choice were low dose (≤ 1600 mg/day) ibuprofen or a nonacetylated salicylate because of their relatively good gastrointestinal and renal safety profiles, respectively. The effectiveness of ACET and various NSAID in relieving OA symptoms was generally considered comparable.

Since publication of the 1995 Guidelines, the above premises have been reevaluated. The newer COX-1 sparing NSAID, celecoxib and rofecoxib, appear to cause no more gastrointestinal injury or serious adverse GI events than placebo. In addition, well tolerated high dose proton pump inhibitors appear to be about as effective as misoprostol in preventing NSAID induced gastric ulcers[4]. However, each of these strategies for reducing NSAID gastropathy is associated with substantial medication costs, and none fully addresses the problems of NSAID nephropathy, e.g., fluid retention, blood pressure elevation, attenuation of the efficacy of antihypertensive drugs, heart and/or kidney failure, and hyperkalemia, the risks of which are probably as great with the newer agents as with nonselective NSAID. Therefore, overall safety and cost issues continue to weigh in favor of ACET as a first line drug for palliation of OA pain.

The comparative efficacy of ACET and NSAID in management of OA pain has been questioned in several

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Supported in part by NIH grants AR39250 and AR20582.

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Submitted June 26, 2000 revision accepted October 18, 2000.

recent studies including a patient preference survey[5]; a 6 day randomized, parallel comparison of ACET 1000 mg 4 times daily versus ibuprofen 400 mg 3 times daily[6]; and a 6 week crossover comparison of ACET 1000 mg 4 times daily versus diclofenac 75 mg/misoprostol twice daily[7]. Each of those studies suggested ACET is inferior to NSAID for relief of OA pain. However, the patient preference survey and the diclofenac versus ACET crossover study yielded a remarkably consistent finding: about 45% of the patients felt that ACET was superior to, or about as effective as NSAID. Furthermore, perceptions with respect to the effectiveness of ACET increased with the age of the patient, which is a relevant point because OA is chiefly a disease of the elderly[5].

In the 6 day parallel ACET versus ibuprofen study, 693 patients with knee OA were stratified into those with mild to moderate pain and those with moderately severe to severe pain at baseline. Among those with milder pain, outcomes with the 2 treatments were comparable. However, in patients with more severe knee pain, ibuprofen was statistically superior to ACET for palliation of walking pain and overall efficacy.

Subsequent to the reporting of the above mentioned 6 day study, Moskowitz presented a Proposed New Schema for Treatment of Knee OA in a symposium at the 1999 American College of Rheumatology meeting. His algorithm, published on the Internet[8], recommends a COX-1 sparing NSAID or a nonselective NSAID, with or without coadministration of a gastroprotective agent, as the first choice drug for patients with moderate to severe OA pain, and limits ACET use to those with mild to moderate pain. To evaluate the relevance of this dichotomization, we reanalyzed the data from our 4 week randomized, double blind comparison of low dose ACET and high dose ibuprofen as treatment of knee OA[9], to determine any correlations between baseline pain scores and pain outcomes.

MATERIALS AND METHODS

Our previous study[9] involved 184 patients with radiographically mild to moderate knee OA (Kellgren-Lawrence grades 2–3), recruited chiefly from primary care clinics. Overall knee pain was assessed by the horizontal, double anchored visual analog scale (VAS) included in the Health Assessment Questionnaire (HAQ)[10]. An identically arrayed and anchored VAS was used to quantify rest pain and walking pain. All VAS measurements were converted to a 0 (none) to 3 (severe) scale using the standard technique[10]. The patients' baseline assessment of their overall knee pain (HAQ) ranged from mild to severe at the end of a 3–7 day washout from analgesics and NSAID. Patients were allowed to use propoxyphene hydrochloride, up to 65 mg 4 times daily, for pain during the washout period, but not within 24 h of their baseline visit or subsequently during the study. They were then randomized to treatment with identical appearing tablets of ACET 500 mg, ibuprofen 150 mg, or ibuprofen 300 mg, each of which was administered as 2 tablets 4 times daily. Followup evaluation was performed at the end of 4 weeks of treatment. As in the original report, this analysis includes the 182 participants for whom followup outcome data were available (n = 60, 61, and 61 for ACET, ibuprofen 1200 mg/day, and ibuprofen 2400 mg/day, respectively).

To address the question: "Does baseline pain severity have a differential effect on the response to the 3 treatments?" we examined the Pearson correlation coefficients between the baseline (post washout) scale and the absolute change after treatment for each of the pain variables (HAQ, resting, walking). Because it is a function of the baseline value, a correlation is introduced by calculation of the change score. To avoid this inherent correlation, we examined the correlations between the baseline pain score and the other 2 change scores (e.g., between the baseline HAQ pain score and the change in rest pain or change in walking pain). If baseline pain values differentially affected treatment associated change scores, i.e., treatment effectiveness, we would expect these correlation coefficients to differ among the 3 treatment groups.

Additionally, we divided the entire study population roughly into tertiles to form groups with low, medium, and high baseline pain severity for each measure. The cutoff points for low severity were ≤ 1.0, 0.5, and 0.8 for HAQ, resting, and walking pain, respectively. Scores were classified as high severity if they were above 2.0, 1.6, and 1.9 for HAQ, resting, and walking pain, respectively. We sought treatment related differences between the means of changes in pain scores (HAQ, resting, walking) within each of the 3 levels of baseline pain severity (low, medium, high). These pairwise comparisons were performed using t statistics without adjustment for multiple comparisons.

Finally, 2 factor analysis of variance (ANOVA) models, which included treatment group, pain severity group, and their interaction, were fit for each group. A significant interaction would provide strong evidence of a differential drug treatment response related to the baseline pain severity level.

RESULTS

Statistically significant correlations were found for each pain measure within each treatment, i.e., a higher baseline pain score was associated with a greater decrease in pain with treatment ($p \leq 0.003$ for all, data not shown). These correlations appeared to be similar across the 3 treatment groups. As shown in Table 1, correlation coefficients across pain measures, although rather weak, were significant somewhat more often in both ibuprofen treatment groups than in the ACET group.

Examination of the mean change scores for each pain measure by treatment group and baseline pain severity

Table 1. Correlation coefficients (p values) between differing baseline and change scores.

Baseline	Change	ACET 4000 mg/day	Ibuprofen 1200 mg/day	Ibuprofen 2400 mg/day
HAQ pain	Rest	0.244 (0.060)	0.302 (0.019)	0.270 (0.036)
	Walk	0.294 (0.022)	0.237 (0.069)	0.305 (0.017)
Resting pain	HAQ	0.110 (0.40)	0.321 (0.013)	0.239 (0.063)
	Walk	0.216 (0.097)	0.187 (0.15)	0.389 (0.002)
Walking pain	HAQ	0.208 (0.11)	0.316 (0.014)	0.192 (0.14)
	Rest	0.145 (0.27)	0.186 (0.15)	0.305 (0.017)

revealed statistically significant superiority of ibuprofen 2400 mg/day compared to the other 2 treatments for resting pain (p = 0.039), but not for walking pain or HAQ pain, and only in the high baseline pain group (Table 2). This difference was nominally significant without adjustment for multiple tests, and would not be significant after adjustment for multiple hypothesis testing.

The results of the ANOVA models are presented in Table 3. Although there was a significant difference in pain relief based on the initial pain score, the analyses did not show a significant treatment effect for any of the pain measures. Most importantly, there were no significant interactions between treatment group and baseline pain severity for any of the 3 pain measures examined (p values for HAQ, resting, and walking pain = 0.95, 0.20, and 0.47, respectively). Because the study was originally powered to detect a significant treatment effect, we performed power calculations to determine our ability to detect an interaction. Based on the observed standard deviation and a 5% significance level, our study has 80% power to detect a significant interaction if the 3 treatments had the same efficacy in the groups with low and medium pain severity, but pain reduction of ≥ 0.5 units in the high pain group with either of the 2 ibuprofen treatments, relative to ACET.

Table 3. Analysis of variance results.

Pain Measure	p Values		
	Interaction	Treatment	Baseline Pain Group
HAQ	0.95	0.91	0.0001
Rest	0.20	0.13	0.0001
Walk	0.47	0.31	0.0001

DISCUSSION

This analysis clearly shows that among our patients with knee OA, a higher level of pain at the time treatment was initiated predicted a quantitatively greater decrease in pain with treatment. This was true for ACET and for either the analgesic or antiinflammatory doses of ibuprofen. Further, among patients with a low level of pain at baseline, worsening of pain after initiation of treatment was common with all 3 treatments (Table 3). To some extent, these findings may represent regression to the mean. Inadequate elimination of the NSAID/analgesic effect prior to initiation of study treatment would provide an alternative explanation for the increase in pain among patients who had a low pain score at baseline. Although the washout period for all patients was at least 5 half-lives of the drug whose use was halted, persistent benefit for periods far exceeding 5 serum half-lives has been observed after discontinuation of NSAID therapy[11]. Similarly, a differential carryover effect of drug treatment could, in part, explain the findings in the diclofenac/misoprostol versus ACET study, in which the washout period between active treatments was 7 days[7].

The 6 day ibuprofen versus ACET study[6], which showed superiority of an analgesic dose of ibuprofen 1200 mg/day to ACET 4000 mg/day among patients with moderately severe to severe OA pain, has characteristics of an acute pain model. This study design accentuates differences between analgesics with respect to pharmacokinetics and pharmacodynamics[12]. While it may be rational to use an NSAID for only brief periods to relieve OA pain, this is generally not how NSAID are prescribed, and the relevance of a 6 day pain study to management of the chronic pain of OA is unclear.

Among our patients, ACET was as about effective as either an analgesic dose or an antiinflammatory dose of ibuprofen in treating the full spectrum of pain associated with knee OA. We have previously shown that the presence of knee swelling and tenderness did not predict a preferential response to an NSAID, relative to ACET, in patients with knee OA[13]. Such signs of inflammation also fail to predict the response to an intraarticular injection of corticosteroid[14]. Obviously, for the patient with OA with acute joint swelling, tenderness, and effusion, arthrocentesis for diagnostic and therapeutic purposes is appropriate. If infec-

Table 2. Mean change scores by treatment and baseline pain severity.

Pain Measure	Baseline Pain Severity	ACET 4000 mg/day	Ibuprofen 1200 mg/day	Ibuprofen 2400 mg/day
HAQ	Low	–0.02	–0.17	–0.16
	Medium	0.42	0.32	0.44
	High	0.61	0.70	0.69
Resting	Low	–0.25	–0.05	–0.29
	Medium	0.05	0.47	0.40
	High	0.48	0.51	0.97*
Walking	Low	–0.28	–0.02	–0.09
	Medium	0.36	0.19	0.33
	High	0.42	0.83	0.86

*Improvement in the ibuprofen 2400 mg/day group was significantly greater than the ACET group (p = 0.047) and the ibuprofen 1200 mg/day group (p = 0.039). However, the differences did not persist after adjustment for multiple comparisons.

tion is excluded, intraarticular corticosteroid injection should be considered, even if the benefits are likely to be short-lived[15]. However, because of its favorable toxicity profile, low cost, and reasonable efficacy, the evidence supports the recommendation that ACET is the pharmacologic agent of choice for initial drug therapy of symptomatic knee OA, regardless of the level of joint pain or presence of signs of inflammation.

Our data suggest that as judged by patients with OA, ACET will be about as effective as NSAID in nearly 50% of cases. If, in conjunction with implementation of nonpharmacologic measures aimed at protecting, stabilizing, and reducing loading of the damaged joint, patients do not experience improvement within 3–4 weeks, it is reasonable to modify the treatment to include an NSAID, with or without a gastroprotective agent.

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