Editorial

Should the Initial Drug Used to Treat Osteoarthritis Pain Be a Nonsteroidal Antiinflammatory Drug?

The 1995 American College of Rheumatology (ACR) guidelines for medical management of osteoarthritis (OA) of the hip contain the following unambiguous recommendation: "...comparing efficacy, safety...and cost, acetaminophen (ACET) should be considered the preferred first-line pharmacologic therapy for patients with symptomatic OA of the hip."[1] This recommendation was based on the view that "...toxicity is the major reason for not recommending the use of nonsteroidal antiinflammatory drugs (NSAID) as first-line therapy for patients with OA."[1] The principles of pharmacologic therapy for patients with symptomatic OA of the knee were considered to be similar to those for patients with OA of the hip[2].

In 1998, the ACR established an *ad hoc* committee comprising 4 of the 8 authors of the 1995 recommendations to update the Guidelines. The results of their deliberations, which have recently been published[3], are important insofar as they carry the imprimatur of the prestigious ACR and will influence managed care organizations, formulary committees, and practicing physicians.

In a clear departure from the 1995 recommendation, the new ACR guidelines state: "In patients with knee OA with moderate-to-severe pain, and in whom signs of joint inflammation are present...prescription of an NSAID merits consideration as an alternate (i.e., alternative to ACET) initial therapeutic approach." This contrasts not only with the 1995 ACR Guidelines, but with the conclusion of a group of experts in the United Kingdom who systematically reviewed the published evidence and recommended that "initial treatment for painful joints attributed to degenerative arthritis [i.e., OA] should be paracetamol [i.e., ACET] in doses of up to 4 g daily."[4] Similarly, guidelines published recently by the European League Against Rheumatism (EULAR) conclude that "paracetamol [ACET] is the oral analgesic to try first and, if successful for management of knee OA, is the preferred long-term oral analgesic."[5] Further, the EULAR document states that although "NSAIDs would appear a logical drug in patients unresponsive to paracetamol, particularly in the presence of clinically overt synovitis, no direct evidence base (exists) to support this statement." And, consistent with the latter guidelines, a current compendium of evidence of the effects of clinical interventions, based on thorough searches and evaluation of the literature, states: "We found no good evidence that NSAIDs are superior to simple analgesics such as [ACET], or that any of the many NSAIDs is more effective than the others in relieving the pain of osteoarthritis."[6]

It is notable that following publication of the 1995 ACR guidelines, which recommended ACET as the initial drug of choice for OA pain[1,2], NSAID that specifically spare cyclooxygenase-1 (COX-1), coxibs, were approved by the US Food and Drug Administration (FDA) for symptomatic treatment of OA pain. Following this approval, the manufacturers of celecoxib and rofecoxib initiated vigorous and highly successful campaigns promoting these agents to consumers and physicians. As a result, the use of NSAID in general and of coxibs in particular by patients with OA has increased dramatically. Marketing research indicates that since COX-1 sparing NSAID have become available in the United States, the total number of NSAID prescriptions for persons over the age of 65 years (in whom OA pain is a predominant indication for prescription of an NSAID) has grown, so that in the spring of this year more than 50% *of all NSAID prescriptions* for patients in this age group who were "new to NSAID therapy," i.e., who had not had a prescription for an NSAID filled in the past 12 months, were written for a COX-1 sparing agent[7].

In a recent symposium (sponsored by an educational grant from pharmaceutical companies marketing a new COX-1 sparing NSAID), a summary of which was published on the Internet[8], it was contended that "...COX-2-specific or traditional NSAID with gastroprotective agents are likely to provide greater benefit [than ACET] in such patients." How pain severity was defined is unclear, nor was a recommendation made with respect to how the physician might reliably quantify the severity of OA pain in the context of a busy clinical practice.

In response to questions about their own approach to therapy, 62% of the nearly 450 rheumatologists attending this symposium indicated that ACET would be their initial treatment for a 65-year-old woman with a history of chronic knee OA with no synovial swelling or tenderness; 35% stated they would have prescribed an NSAID. However, if the same patient with OA had "morning stiffness, mild effu-

sion and tenderness to palpation," only about 5% indicated they would initially prescribe ACET, while about 75% would now recommend an NSAID[8].

Who is right? Industry? The new ACR Guidelines? The other OA Guidelines? The physicians who are currently prescribing coxibs for OA patients with extraordinary frequency? Is the paradigm shift exemplified above, with expansion of NSAID use to include initial pharmacotherapy for OA pain, supported by the evidence? This paper examines the data and the gaps in our knowledge relevant to that question.

It should be noted that clinical trials of the coxibs have been largely supported by the manufacturers. Rochon, *et al*[9] found that commercially funded studies of drug therapy of OA are significantly more likely to support the intervention under investigation than similar studies that are not funded by industry. In addition, examination of the results of clinical trials, as ascertained from reports submitted to institutional review boards, reveals that studies that yield "significant" results are much more likely to be published than those that do not[10,11]. Further, this publication bias was found to originate chiefly with the investigators, rather than journal editors: only 6 of 124 unpublished studies were reported to have been rejected for publication[10]. Publication bias and commercial funding bias may thus affect the recommendations of OA guidelines committees attempting to formulate recommendations based on the available evidence. It is particularly important, therefore, that individuals charged with developing treatment guidelines differentiate evidence based recommendations from expert opinion. Failure to do so represents a serious deficiency in the recent revision of the ACR Guidelines.

ARE SIGNS OF JOINT INFLAMMATION AN INDICATION FOR AN NSAID AS THE INITIAL DRUG FOR OA?

Few studies have directly compared ACET to placebo in patients with knee OA. Amadio and Cummings[12] documented the superiority of ACET (4000 mg/day), relative to placebo, in a 6 week randomized double blind crossover study of 25 patients with symptomatic knee OA. Global evaluations by both patient and investigator revealed significantly greater improvement with ACET than with placebo, and although signs of inflammation (joint swelling and warmth) were not affected by ACET, the drug significantly reduced the time required to walk 50 ft, reflecting also functional improvement.

There is no question that NSAID provide superior efficacy to ACET in some patients with knee OA[4,13-16]. Randomized clinical trials comparing a simple analgesic to an NSAID in patients with OA of other joints (e.g., hand, hip, spine) are not available. However, there is presently no way to predict in which OA patient an NSAID will be more effective than ACET. In particular, there is no evidence that NSAID are more effective in patients whose OA pain is associated with clinical signs of joint inflammation than in those in whom it is not. For example, an antiinflammatory dose of ibuprofen (2400 mg/day) was not significantly more effective than an analgesic dose of that drug (1200 mg/day) or than ACET (4000 mg/day) in patients with knee OA[17]. A secondary analysis of the results of that study showed that either of these analgesic regimens was as effective as the antiinflammatory dose of ibuprofen even among patients who had joint tenderness or swelling[18]. Indeed, these signs of inflammation also fail to predict the response to intraarticular injection of corticosteroid[19]. However, trends for walking pain and rest pain in the comparative trial of ibuprofen and ACET mentioned above[17] favored the antiinflammatory dose of ibuprofen over the analgesic dose and the latter over ACET; it is possible that a larger sample size would have revealed statistically significant, or even clinically significant, differences between treatment groups.

On the other hand, a low dose of ibuprofen, 1200 mg/day, was as effective as the very potent antiinflammatory drug, phenylbutazone, 400 mg/day, in relieving symptoms of knee OA among 133 subjects who completed a 4 week randomized parallel double blind trial[20]. In a double blind crossover study in 30 patients with OA of the hip, knee, or spine, in which each treatment period was 3 weeks, an analgesic dose of ibuprofen (900 mg/day) was as effective as an antiinflammatory dose of the NSAID sodium meclofenamate (300 mg/day)[21]. Similarly, in a study of similar design in which 18 of the 30 patients who entered the trial completed one month of treatment with each drug, the analgesic nefopam was as effective as the NSAID flurbiprofen[22]. It should be pointed out that the sample size in these studies was relatively small and subjects were not characterized with respect to clinical signs of joint inflammation.

IS INCREASED SEVERITY OF KNEE PAIN AN INDICATION FOR AN NSAID AS THE INITIAL DRUG FOR OA?

Contrary to the implication in the Internet publication cited above[8] — increased severity of walking pain, rest pain, or overall pain at baseline did not predict a significantly better response to an antiinflammatory dose of ibuprofen than to ACET in a secondary analysis of the results of a 4 week trial in patients with knee OA[23]. This contrasts with the results of a recent 6 day randomized, double blind parallel design study in patients with knee OA in whom an analgesic dose of ibuprofen, 1200 mg/day, was statistically superior to ACET, 4000 mg/day, in reducing the severity of pain on walking and in overall efficacy among those who had moderately severe to severe joint pain at baseline, but not in those with mild to moderate pain[24]. The brief duration of this study, however, imbues it with features of an acute pain model, in which pharmodynamic and pharmacokinetic differences between analgesics may be accentuated[25]. The

relevance of the results to management of the chronic pain of OA, therefore, is unclear.

What, then, is the basis for the widely held view that the usefulness of ACET in management of OA is limited to treatment of *mild-to-moderate* pain? Certainly, few would consider ACET an effective analgesic for management of the severe pain due, e.g., to a ruptured aneurysm, kidney stone, or bony metastasis. However, other than the two studies cited above[23,24], we have found no reports examining the effectiveness of ACET or NSAID in relation to the severity of OA pain. The view that ACET is not an effective analgesic in patients with more severe OA pain is reinforced by the information on Tylenol® in the Physicians' Desk Reference[26], which states that the product is indicated for "minor arthritis pain." This language is required by the FDA for *all* over-the-counter analgesics used for joint pain. With the exception of the 6 day clinical trial cited above[24], there is no evidence that ACET is less effective in patients whose OA pain is greater than "minor" or "mild-to-moderate." Indeed, the study by Bradley, *et al*[23] cited above suggests that this is not the case. More studies are needed to answer this question.

HOW EFFECTIVE ARE NSAID IN TREATING OA PAIN?

Given the enthusiastic use of coxibs in treatment of OA, it should be noted that celecoxib and rofecoxib are no more effective in treating OA pain than nonselective NSAID, such as ibuprofen, diclofenac, or naproxen[27-31]. Indeed, the impact of NSAID on OA pain is, on average, only modest. The magnitude of reduction in joint pain and improvement in mobility with NSAID use is only about 20–25%, relative to the baseline value, with 10–20% differences between NSAID and placebo[32,33]. This (in addition to adverse events) accounts, in part, for the limited satisfaction with NSAID treatment of OA pain shared by patients and physicians and helps explain the observation by Scholes, *et al*[34] that only 15% of patients with OA for whom an NSAID was prescribed were still taking the same NSAID 12 months later. This high rate of discontinuation is seldom observed in the artificial environment of a randomized clinical trial.

Comparable data relative to durability of use are not available for ACET. In a 2 year clinical trial of naproxen versus ACET, in which the overall dropout rate was about 65%, the proportion of patients discontinuing treatment because of poor efficacy was somewhat greater with ACET than with the NSAID, while the proportion discontinuing because of adverse events was greater with the NSAID than with ACET[35]. On the other hand, in a recently reported blinded multicenter study in France, in which aspirin or ACET (both up to 3 g/day) or ibuprofen (up to 1.2 g/day) were administered for up to 7 days to some 8600 patients with a variety of painful conditions in general practice, abdominal pain and dyspepsia were significantly more common with aspirin than with either of the other two treatments and total gastrointestinal (GI) events, including dyspepsia and abdominal pain, were less frequent with ibuprofen (4% and 2.8%, respectively) than with ACET (5.3% and 3.9%, respectively; $p < 0.035$ in each case)[36].

In our 4 week study in patients with knee OA in which ACET, 4 g daily, was compared with ibuprofen, 1200 or 2400 mg/day, with about 60 patients in each treatment arm, GI adverse events were reported by 16%, 11%, and 23% of each group, respectively, and 5%, 3%, and 10%, respectively, of each group failed to complete treatment because of GI symptoms[17]. Clinical trials now in progress, comparing ACET to COX-1 sparing NSAID over several weeks of treatment, will provide useful comparisons.

In a recent report of a 6 week double blind clinical trial comparing rofecoxib, 12.5 or 25 mg/day, to celecoxib, 200 mg/day, or acetaminophen, 1000 mg/qid, both rofexocib doses were statistically superior to ACET and the higher dose of rofecoxib was statistically superior to celecoxib for relief of joint pain[37]. However, only an abstract of the findings is available at this time and the results reported were limited to the first week of treatment. This study and other clinical trials currently in progress will soon provide useful information about the tolerability, side effect profiles, and efficacy of COX-1 sparing NSAID in comparison with those of ACET. Such data are needed to inform the question of which OA patient will do as well (or better) with ACET as with an NSAID.

HOW SAFE ARE COXIBS IN TREATING OA?

Endoscopic studies have shown that celecoxib and rofecoxib are associated with an incidence of gastroduodenal ulceration much lower than that of comparator NSAID and comparable to that of placebo[38]. Large scale clinical trials designed to ascertain whether the striking gastroprotective effect that is seen endoscopically with coxibs is accompanied by a corresponding decrease in the incidence of clinically important GI bleeding, obstruction, and perforation have recently been completed. In a recent summary of data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) Trial, which involved more than 8000 patients with rheumatoid arthritis (RA) and compared rofecoxib, 50 mg/day, to naproxen, 500 mg/bid, the incidence of upper GI perforations, obstructions, bleeding, and symptomatic ulcers was reduced by more than 50% in the rofecoxib group, in comparison with the naproxen group ($p < 0.001$) (Merck and Co., Inc., data on file). The results of this study have not yet been published in a peer reviewed journal.

However, data from the Celecoxib Longterm Arthritis Safety Study (CLASS), a double blind randomized controlled trial in which more than 8000 patients with OA or RA were enrolled and some 4500 (57%) continued treatment for 6 months, have recently been published[39]. Patients were randomly assigned to receive celecoxib, 400 mg bid

(i.e., 2 times and 4 times the maximum dose for RA and OA, respectively); ibuprofen, 800 mg tid; or diclofenac, 75 mg bid. The annualized incidence rates for upper GI ulcer complications (bleeding, perforation, and obstruction) for celecoxib versus NSAID were 0.76% and 1.45%, respectively ($p = 0.09$, i.e., not a statistically significant difference), although those rates for upper GI complications in patients who also had symptomatic ulcers were 2.08% and 3.54%, respectively ($p = 0.02$). Among those taking low dose aspirin (about 20% of the subjects) the annualized incidence rate for upper GI ulcer complications in the celecoxib treatment group was not different from that for subjects treated with a nonselective NSAID.

Of further relevance to selection of the initial pharmacologic agent for treatment of OA pain, even if COX-1 sparing NSAID significantly reduce the incidence of gastroduodenal ulceration and clinically important GI bleeding, obstruction, and perforation, their safety is less favorable than that of ACET when both are used in recommended doses. It is clear that COX-1 sparing NSAID — like nonselective NSAID, and in contrast to therapeutic doses of ACET — are associated with important adverse effects, such as renal insufficiency, fluid retention, hyperkalemia, hypertension, congestive heart failure, and interference with the effect of some antihypertensives[40,41]. In an analysis of several double blind randomized trials that varied with respect to treatment duration, comparator NSAID, and inclusion of a placebo group, the cumulative incidence of nonspecific GI adverse events (e.g., dyspepsia, abdominal pain, epigastric discomfort, nausea, heartburn) was only slightly lower with rofecoxib than with nonselective NSAID over a 6 month treatment period (23.5% vs 25.5%; $p = 0.02$), and no lower than that with nonselective NSAID thereafter[42]. This difference between groups in the first months of treatment, even though statistically significant, cannot be considered *clinically* significant. Furthermore, no statistically significant difference was apparent between treatment groups with respect to nonspecific GI complaints leading to discontinuation of therapy.

WHAT ABOUT PATIENT PREFERENCES FOR NSAID IN COMPARISON WITH ACET?

How often will the OA patient do better with an NSAID than with ACET? Three recent studies speak to this question: Pincus, *et al*[43], analyzing the results of a 15 minute telephone survey, found that among 150 patients presumed to have OA (medical records and/or radiographs were not available to confirm the diagnosis in an unspecified proportion of these subjects) who had taken ACET and had named a drug as "most helpful," some 21% stated that this drug was ACET, 73% felt it was an NSAID, and 6% designated some other analgesic. Significantly higher rates of drug discontinuation because of toxicity were seen with NSAID than with ACET. The authors concluded that ACET "...was an appropriate choice for some patients with OA..." but "...may not be an optimal choice for many patients."

Second, in a recent survey of 668 patients with hip or knee OA who were asked to rate the effectiveness of, and their overall satisfaction with, ACET in comparison with NSAID they had received, about 45% reported that ACET was about as effective as, or more effective than, their NSAID[13]. A comparable proportion reported they were as satisfied, or more satisfied, with ACET as with their NSAID. Furthermore, the proportion of patients expressing a preference for ACET increased with age. The authors concluded that, "if safety and cost are issues, ...the [ACR] recommendation that ACET be tried first seems correct...."

Third, in a 6 week double blind crossover study comparing a diclofenac/misoprostol formulation with ACET in patients with OA of the hip or knee, even though the magnitude of improvement in joint pain, function, and quality of life was greater with the NSAID, 22% of the patients reported no difference between the two drugs and an additional 20% found ACET to be "better" or "much better" than diclofenac/misoprostol (Pincus T, personal communication). Ratings of overall efficacy by the physician were similar to those by the patient.

In considering the initial recommendation of a drug for symptomatic treatment of OA pain, both the patient and physician should be aware that, as noted above, existing data indicate that nearly 50% of patients with OA pain may find ACET as effective as a nonselective NSAID (and hence presumably as effective as a COX-1 sparing NSAID). Furthermore, COX-1 sparing NSAID are much more expensive than ACET (Table 1). However, studies comparing the cost effectiveness of ACET and NSAID in OA are not available.

Because of their apparent lack of effect on the GI mucosa and the platelet, COX-1 sparing NSAID represent an important expansion of the pharmacologic options available for treatment of OA symptoms. In view of their limited efficacy, adverse effects, and cost, however, they should not be considered the "standard of care" for *initial* treatment of OA pain. Additional studies that address the relative merits of antiinflammatory and analgesic drugs in symptomatic treatment of OA are needed. Nonetheless, a considerable body of evidence exists that can inform the physician intending to prescribe pharmacologic therapy for relief of OA pain. Based on this evidence, we would conclude that there is no reason to modify the recommendations in the 1995 ACR Guidelines: ACET is the drug of choice for initial treatment of OA pain — regardless of the severity of joint pain or the presence of clinical signs of joint inflammation.

This is not to say that ACET is the only pharmacologic agent needed for palliation of OA pain. If sufficient improvement does not occur within a reasonable time (e.g., 4 weeks) after initiation of treatment with ACET and appropriate nonpharmacologic measures, addition of a low dose

Table 1. Approximate retail cost, in US dollars, for 30 days of treatment of OA pain with variou regimens*.

	Pharmacy A	Pharmacy B	Pharmacy C	Pharmacy D
Acetaminophen, generic, 3 g/day				
Tablets	11.14	7.18	8.98	8.98
Caplets	11.14	7.18	8.98	8.98
Gel caps	11.86	7.18	10.60	10.78
Celecoxib, 200 mg/day	73.04	62.99	84.00	72.99
Rofecoxib, 12.5 mg/day	73.13	70.20	84.00	74.55
Rofecoxib, 25 mg/day	73.14	70.20	84.00	74.55
Naproxen, generic, 750 mg/day	20.39	16.59	26.29	17.90
Naproxen, generic, 1,000 mg/day	20.69	19.99	30.59	23.99
Naproxen, generic, 1,000 mg/day + misoprostol, 800 µg/day	138.78	135.96	172.58	146.38
Naproxen, generic, 1,000 mg/day + omeprazole, 20 mg/day	141.98	123.28	155.58	139.98

* Retail prices in 4 Indianapolis pharmacies, January, 2000.

of NSAID (e.g., ibuprofen, 1200 mg/day; naproxen, 500 mg/day) is reasonable. When risk factors for serious adverse GI side effects of NSAID are present, a COX-1 sparing NSAID may be preferable to even a low dose of a nonselective COX inhibitor and would be much cheaper than a nonselective NSAID and co-therapy with either misoprostol or omeprazole (Table 1)[44-47].

If the above approach does not produce sufficient symptomatic relief, many physicians would increase the NSAID dose to an antiinflammatory range. It should be noted, however, there are no data to support this approach. Indeed, the published evidence argues against it[17,20-22]. As indicated earlier, an antiinflammatory dose of ibuprofen was not significantly more effective than an analgesic dose of that drug in ameliorating joint pain in patients with knee OA[17]. In addition, in a double blind 4 week comparison of ibuprofen, 1200 mg/day (an analgesic dose), with ibuprofen, 2400 mg/day (an antiinflammatory dose), in patients with hip or knee OA, no correlation was apparent between dose and clinical outcome[48]. On the other hand, the area under the serum concentration curve and trough serum ibuprofen concentrations were significantly related to improvement in disability and rest pain associated with hip and knee OA, suggesting that some of the individual variation in responsiveness to ibuprofen (and presumably to other NSAID) are attributable to pharmacokinetic differences among patients, rather than to the adequacy of the prescribed dose as an antiinflammatory. We are unaware of studies relating clinical outcomes to variations among patients with respect to the pharmacokinetics of COX-1 sparing NSAID.

The ACR Guidelines and other OA guidelines emphasize that *non*pharmacologic measures are the keystone of management of OA pain[1,2]. Drugs (analgesics, nonselective NSAID, COX-1 sparing NSAID) should serve as an adjunct to those nonmedicinal therapies. Although the effect size of such measures may be relatively modest, their effects may be additive and their use may permit a reduction in the dose of NSAID or analgesic. Mazzuca, *et al*[49] found that the size of the effect of a self-care intervention on rest and pain and disability of patients with knee OA who were taking an NSAID or analgesic was 0.3 of a standard deviation 12 months after the intervention. In a metaanalysis, Superio-Cabuslay, *et al*[50] found that patient education interventions provided additional benefits that were 20–30% as great as the effect of NSAID treatment for OA pain. In a controlled trial, monthly telephone calls from lay volunteers resulted in improvements in joint pain and mobility in patients with knee OA who were taking NSAID, and the magnitude of improvement was nearly as great as that seen in open label trials of NSAID (i.e., the phone call was effective "second-line therapy")[51].

Patients who beseech their physician to prescribe one of the newer NSAID in the hope of gaining greater symptomatic relief should be counseled with regard to the advantages and limitations of these drugs and the importance of understanding that *any* pharmacologic therapy for OA should complement changes in lifestyle, as required to reduce loading of the damaged joint. While acquiescence in the patient's request for one of the new NSAID may be the path of least resistance, it is unlikely to result in substantial longterm improvement unless concomitant nonpharmacologic measures are employed. In an analysis of data from the Women's Health and Aging Study, Pahor, *et al*[52] recently reported that only about 25% of older disabled women who were using ACET for lower body osteoarticular pain were taking a full therapeutic dose of the drug. In our experience, when the utility and limitations of analgesics/NSAID in the overall management of OA pain are put into perspective by the physician, even patients who had found that therapeutic doses of ACET were ineffective for their OA pain before they sought medical attention may now find it satisfactory. Given the constraints imposed by health care delivery

systems today on the time physicians have available for patient education, finding ways to provide such counseling is a major challenge. If we meet that challenge, health outcomes of our patients with OA will be improved.

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