Editorial

Osteoarthritis: Simple Analgesics versus Nonsteroidal Antiinflammatory Drugs

The treatment of osteoarthritis (OA), in concert with the treatment of inflammatory arthritides, has undergone significant advances over the past several decades. Not too many years ago patients with OA were generally ignored, on the bases of myths that the disease was a "nuisance" but never disabling, and that, even if the diagnosis had been made, there were no therapeutic approaches of significant benefit. With the aging of the population — baby boomers growing old, and medicine keeping older people alive longer — we have become aware of the inaccuracy of those myths. OA can be and often is disabling; much can be done to relieve pain and perhaps retard the disease process. In the past year hundreds of thousands of individuals in the United States underwent total hip or total knee replacement for arthritis; the majority of these procedures were performed for OA. It is apparent that better medical care targeting both symptomatic relief as well as disease modification would have great potential for lessening the disability and economic impact of OA on society.

In 1995, the American College of Rheumatology (ACR) appointed an ad hoc subcommittee to develop guidelines for the management of OA[1,2]. These guidelines stressed the importance of a background nonpharmacologic approach, to be utilized not only initially in the care of patients, but throughout the entire course of management. These nonpharmacologic approaches included items such as weight reduction, appropriate exercises to strengthen joint related muscles and to maintain joint range of motion, occupational therapy, avoidance of joint overuse, and appropriate use of orthotics. Medical management recommended the use of simple analgesics as initial therapy, followed by nonsteroidal inflammatory drugs (NSAID) ranging from over-the-counter to full doses depending on the patient's symptomatology and response. Acetaminophen was recommended as the drug of choice for initial therapy based on efficacy, tolerability, and cost issues. The advantage of a trial of acetaminophen as initial therapy was particularly supported by its lesser toxicity compared to full doses of classical, traditional NSAID, which had a less attractive therapeutic/toxicity ratio. Classical NSAID were associated with a high frequency of gastropathy, characterized primarily by upper gastrointestinal ulceration; significant complications included hemorrhage, perforation, and obstruction. Although daily dose and duration of administration of such NSAID bore a relationship to frequency of complications, gastropathy was not infrequently observed, even with over-the-counter doses. Toxicity to traditional NSAID was lessened with the additional administration of gastroprotective agents such as misoprostol or proton pump inhibitors, but at significantly increased cost. Administration of intraarticular corticosteroids represented an important component of therapy, to be used judiciously, and generally on a non-regular basis; it was of particular benefit for individuals with acute flares.

Investigational therapies such as tidal lavage and electromagnetic stimulation remained investigational. Surgical approaches, particularly total joint replacement, were of significant benefit for relief of pain and improved function in patients with advanced disease.

In 1999, the ACR reassembled a subcommittee on OA Guidelines in response to major advances that had occurred in the intervening few years. NSAID characterized as cyclooxygenase-2 (COX-2) selective inhibitors were reported to have efficacy similar to traditional NSAID, but at significantly decreased risk with respect to gastrointestinal complications. In addition, absence of inhibition of platelet aggregation provided advantage for decreased bleeding, helpful when NSAID were being administered in patients undergoing minor or major surgical procedures. A second advance in therapy related to the introduction of hyaluronans for treatment of OA of the knee. Prescribed courses of injections were associated with pain relief and improved function, often of prolonged degree and with safety confirmed with use of repeated cycles. Accordingly, a

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new set of guidelines was published in September 2000 to provide a revised scheme of recommended therapy for OA[3].

One of the important changes in the revised ACR 2000 guidelines related to the recommendation for initial therapy of the disease. Although it was recommended that acetaminophen still merited consideration for initial use based on efficacy, tolerability, and cost, the safety profile of the new COX-2 selective NSAID now allowed consideration of these agents as initial therapy. Acetaminophen therapy, although effective in a number of patients, may fail to provide adequate response in many individuals, even in full doses. New, direct comparative studies showed that NSAID were more efficacious than acetaminophen[4-6], and that COX-2 selective inhibitors, or classical NSAID administered with gastroprotective agents, merited consideration for initial therapy based on efficacy and an improved safety profile. Their use was considered to be of increased benefit in patients with moderate to severe disease, particularly with associated inflammation.

In the current issue of *The Journal*[7] a post-hoc reanalysis of a paper published in *The New England Journal of Medicine* in 1991[8], "Comparison of an anti-inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee," is revisited. The objective of the reanalysis was to determine whether greater pain intensity at the initiation of treatment predicted better response to ibuprofen than to acetaminophen in subjects with knee OA. Results revealed that greater baseline pain predicted greater pain relief with all 3 treatments. The authors note that subjects with a high level of baseline pain appeared to respond better to ibuprofen at a full therapeutic dose of 2400 mg per day than to acetaminophen, but then comment that the difference was not evident after correction using additional statistical tests.

The authors of this reanalysis have played a leadership role in alerting physicians to the risk of complications of classical NSAID, and, on the basis of this concern, have championed the use of simple analgesics in the treatment of OA. Prudence and caution are always positive attributes in health care delivery, and studies to assess and reassess therapeutic approaches are not without merit. Although, using new statistical testing methods, the authors conclude that acetaminophen and ibuprofen were comparably effective in treating knee OA pain, even when the pain is severe, they provide reference to a study wherein individuals with a high level of baseline pain appeared to respond better to ibuprofen than to acetaminophen[5]. Further, they note that since publication of the 1995 ACR guidelines, a number of studies described superior efficacy of NSAID in the management of OA pain compared to acetaminophen[4,6]. They further comment on the increased safety of COX-2 selective NSAID with respect to serious adverse gastrointestinal events compared to classical NSAID.

The authors refer to my proposed schema for the treatment of knee OA, published on the Internet[9]; this schema recommended a COX-2 selective NSAID, or a nonselective NSAID with or without coadministration of a gastroprotective agent, as the drug of first choice for patients with moderate to severe OA pain, recommending acetaminophen for initial use in those with mild to moderate pain. This recommendation appears counter to their suggestion that acetaminophen is equally efficacious to NSAID at all baseline pain levels, supporting its use as initial therapy in all patients with OA.

The authors and I do not really differ in our approach to management; where we differ is in our interpretation of available data, and in analytic approach. Retrospective statistical pursuit of data, although of interest, is most generally indicated for exploratory hypothesis testing, the results of which can be used for future experimental design. Post-hoc analyses of data with multiple methodologies may lead to supportive but not necessarily valid conclusions. I am in agreement that acetaminophen has a meaningful role in the management of OA, either as initial therapy or as continuing/adjunctive therapy. In patients with mild to moderate pain, I frequently utilize acetaminophen up to maximal dosage as an initial therapeutic trial. Unfortunately, many of these patients, although they receive some benefit, often have inadequate relief or no relief at all. Further, such relief, when present, is often limited in duration as acetaminophen is administered over time. In patients with moderate to severe pain, however, particularly in the presence of inflammation, data show that NSAID may be more efficacious, bringing about more rapid and more definitive relief[4-6]. Such increased relief is likely related to the fact that by the time we see patients with pain from OA, inflammation probably plays a significant role in their symptomatology. Just as one would not treat angina with analgesics without trying to relieve the underlying vasospasm, or migraine headaches with opiates rather than treating the underlying disease process, OA is often better managed treating both pain and inflammation. In patients first receiving acetaminophen who have an inadequate response, nonsteroidal antiinflammatory agents can be added. Similarly, in individuals receiving NSAID as their initial approach to therapy, decreased dosage of NSAID or cessation of therapy and replacement with acetaminophen is often effective in longterm management. Many patients do well with a combination of both NSAID and acetaminophen.

My recommended approach is based on the increased safety of the newer COX-2 selective agents that now provide opportunity for improved efficacy with a higher degree of safety. The availability of intraarticular corticosteroids and intraarticular hyaluronans provides further opportunity for selectivity and individualization of therapeutic approaches. Caveats remain in the use of any of these agents, whether it be liver toxicity with acetaminophen, or

renal toxicity/hypertension concerns with traditional NSAID or the COX-2 selective agents.

As the ACR Committee states, guidelines are recommendations, not rigid mandates — the individual physician is in the best position to decide on therapeutic approaches for each of his/her patients. The voicing of differences in therapeutic philosophy, each based on carefully considered judgments, is healthy, and of benefit to the ultimate recipient — the patient!

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REFERENCES

1. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. I. Osteoarthritis of the hip. Arthritis Rheum 1995;38:1535-40.
2. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. II. Osteoarthritis of the knee. Arthritis Rheum 1995;38:1541-6.
3. Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum 2000;43:1905-15.
4. Wolfe F, Zhao S, Lane N. Preference for non-steroidal anti-inflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1799 patients with osteoarthritis, rheumatoid arthritis and fibromyalgia [abstract]. Arthritis Rheum 1999;42 Suppl:S296.
5. Altman RD. Ibuprofen, acetaminophen and placebo in osteoarthritis of the knee: a six-day double-blind study [abstract]. Arthritis Rheum 1999;42 Suppl:S403.
6. Pincus T, Callahan LF, Wolfe F, et al. Arthrotec compared to acetaminophen: a clinical trial in patients with osteoarthritis of the hip or knee [abstract]. Arthritis Rheum 1999;42 Suppl:S404.
7. Bradley JD, Katz BP, Brandt KD. Severity of knee pain does not predict a better response to an anti-inflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. J Rheumatol 2001;28:1073-6.
8. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an anti-inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991; 325:87-91.
9. Moskowitz RW, Smith JA. Issues in osteoarthritis care: concepts and controversies. Available at http://www.medscape/rheumatology/treatment update/1999/tu03/pnt tu03.html, 1/20/00.