

Nonrheumatologists Wary of NSAIDs for Kids

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Many physicians who care for children say that selective cyclooxygenase-2 nonsteroidal anti-inflammatory agents have equivalent or greater safety, efficacy, or tolerability and fewer side effects than do traditional NSAIDs. However, in the years since the voluntary withdrawal of rofecoxib and valdecoxib from the market, few practitioners aside from rheumatologists prescribe selective COX-2 NSAIDs for children, according to survey results.

The aim of the survey was to examine the prescribing habits of NSAIDs among pediatric medical and surgical practitioners, and to examine concerns and barriers to their use. A link to a 22-question Web-based survey that could be completed in 10-15 minutes was sent to 1,289 pediatricians, pediatric rheumatologists, sports medicine physi-

cians, pediatric surgeons, and pediatric orthopedic surgeons. Eighty-four e-mails were returned as "undeliverable."

Only 338 (28%) of the 1,205 e-mail recipients completed the surveys. The highest response rates were from pediatric rheumatologists (100 of 247, 40%) and the lowest from sports medicine specialists (12 of 106, 11%).

Indeed, one limitation of the study was that it was skewed to include a large percentage of pediatric rheumatologists, according to Dr. Deborah M. Levy, a pediatric rheumatologist at the Hospital for Sick Children in Toronto, and Dr. Lisa F. Imundo, a pediatric rheumatologist at the Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University.

Of the pediatricians and pediatric subspecialists, 98% indicated they had prescribed an NSAID for a child. The most common reasons given for ever prescribing an NSAID were

musculoskeletal pain, soft-tissue injury, fever, arthritis, fracture, and headache.

Nonrheumatologists frequently (more than once a week) prescribed ibuprofen, naproxen, and ketorolac, but they rarely prescribed any other NSAID. Rheumatologists used a wider variety of medications, most notably ibuprofen, diclofenac, indomethacin, naproxen, celecoxib, and rofecoxib.

About half of the respondents (164 of 330) had never prescribed a selective COX-2 NSAID. By specialty, 72% of pediatricians, 52% of orthopedic surgeons, 79% of pediatric surgeons, and 4% of rheumatologists had never prescribed a selective COX-2 NSAID. The most common reasons for prescribing a selective COX-2 NSAID were for arthritis, musculoskeletal pain, soft-tissue injury, and fracture. Use of these agents was more likely after failure of one or more traditional NSAIDs.

Responses from pediatric

rheumatologists showed that certain adverse events were more common with conventional NSAIDs than with selective COX-2 agents. Specifically, abdominal pain (81% vs. 23%), epistaxis (13% vs. 2%), easy bruising (64% vs. 8%), headaches (21% vs. 1%), and fatigue (12% vs. 1%) were more common with traditional NSAIDs (n = 99) compared with the selective COX-2 medications (n = 95).

COX-2 NSAIDs were rated as equivalent or superior to traditional NSAIDs for safety (66%), pain relief (72%), relief of inflammation (74%), and tolerability (83%).

Eleven physicians reported that one or more patients had a cardiovascular event while taking an NSAID. The events were attributed to the patients' underlying diseases, and not to the use of either a traditional or selective COX-2 NSAID, according to the investigators.

Rofecoxib was voluntarily

withdrawn from the market in September 2004 and valdecoxib was withdrawn in April of 2005, and these events affected physician prescribing habits. For pediatric rheumatologists, 57% said they prescribed selective COX-2 NSAIDs less frequently and 26% said they no longer prescribed them. Consequently, 44% increased their prescriptions of traditional NSAIDs.

Nine traditional NSAIDs (aspirin, etodolac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen, oxaprozin, and tolmetin) and one selective COX-2 NSAID (celecoxib) currently have Food and Drug Administration-approved pediatric indications. At the time of the survey, no COX-2 NSAID had a pediatric indication. ■

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EXPERT COMMENTARY

Data Link Periodontitis to Rheumatoid Arthritis

Periodontitis may be a significant trigger of rheumatoid arthritis. My associates and I recently reported preliminary evidence suggesting that this link exists and that further study is warranted.

Our recent analyses used data collected from nearly 16,000 participants of the ARIC (Atherosclerosis Risk in Communities) study. This study, begun in the late 1980s, recruited people aged 45-64 years at four U.S. sites. Investigators followed participants for more than a decade, and 6,661 of the original participants underwent a dental work-up for periodontitis during their final study visit.

Of those who had this dental examination, 33 had a subsequent, first-time hospital discharge for rheumatoid arthritis; we considered them incident RA cases.

In an analysis that controlled for age, sex, and cigarette smoking, participants with moderate or severe periodontitis had a statistically significant, 2.6-fold increased risk of incident RA, compared with people with no or mild periodontitis. Of those 33 incident RA cases, 27 were in the 4,288 people with moderate or severe periodontitis.

Because smoking is the only well-established risk factor for RA, we did a second analysis that divided the participants into subgroups of never-smokers and ever-smokers. Among the more than 2,900 never-smokers, people with moderate or severe periodontitis were 8.8-

fold more likely to develop RA, compared with those who had no or mild periodontitis, a statistically significant difference. In contrast, among the more than 3,700 ever-smokers, the impact of periodontitis was blunted. Smokers with moderate or severe periodontitis had a small (30%) but not statistically significantly increased risk for incident RA, compared with smokers with mild or no periodontitis.

When we examined available serum, we found that among 20 participants with RA and moderate or severe periodontitis, 10 had antibodies to cyclic citrullinated peptide (CCP), and their average antibody titer was more than 20-fold higher than the average anti-CCP antibody titer in 9 people with mild or no periodontitis. This finding is important because the appearance of anti-CCP antibodies has been shown to precede clinical RA (Arthritis Rheum. 2003;48:2741-9; Arthritis Rheum. 2004;50:380-6; Ann. Rheum. Dis. 2008;67:801-7) and these antibodies are also a marker for more severe RA.

The hypothesis that the chronic inflammatory milieu of periodontitis allows production of an anti-citrullinated self-protein immune response was proposed in a review (Inflammation 2004; 28:311-8). This localized autoimmune response could then expand to include both the periodontal space and the joints. A periodontal pathogen that may trigger this

process, *Porphyromonas gingivalis*, makes an enzyme that results in citrullination of proteins. About 12% of the U.S. population is estimated to have periodontitis by age 45 years (J. Periodontol. 1999;70:13-29) making this a plausible, common, and persistent environmental risk that could trigger RA in people with genetic and possibly other environmental risk factors for the disease.

My associates and I reported our findings at the 2009 EULAR Congress in Copenhagen. At that same meeting, Dr. Codrina Ancuta and her colleagues also reported higher anti-CCP antibody titers in a group of RA patients with concomitant periodontitis than those found in a comparison group of RA patients without periodontitis. They further reported that periodontitis severity improved in those RA patients who were treated with a tumor necrosis factor inhibitor.

Recent data suggest that the converse may also be true: Treatment of periodontitis with scaling and root planing—the standard conservative approaches to this condition—improved DAS28 and erythrocyte sedimentation rate in a small group of RA patients with periodontitis (J. Periodontol. 2009;80:535-40).

These apparent relationships between the treatment effects of each condition upon the other raise interesting possible explanations for prior data on the effects of minocycline on RA. Treatment of periodontitis with minocycline has been shown to reduce the oral bacterial load of so-called red-complex bacteria, which

includes *Porphyromonas gingivalis* (J. Periodontol. 2007;78:1568-79). Although the anti-matrix metalloproteinase activity of minocycline is a possible explanation for its efficacy in RA, the antibacterial periodontitis treatment effects may better explain the previously observed enhanced effect of minocycline treatment on early seropositive RA patients (Arthritis Rheum. 1999;42:1691-5).

Taken together, these observations suggest a possible approach for early intervention to prevent RA. We would propose screening periodontitis patients with a family history of RA for anti-CCP antibodies. Those anti-CCP positive individuals who consent to intervention would undergo treatment with a standard procedure for periodontitis (scaling and root planing), with randomization to treatment with the antibiotic minocycline vs. placebo. Such a study could assess the impact of minocycline on periodontitis progression, and on the incidence of new RA cases in a population likely to be at high risk of progression to RA.

At a minimum, results from such a study should yield an estimate of the prevalence of anti-CCP antibodies and incidence of RA in this presumably high-risk population, and help in the design of further early RA intervention studies. ■

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