Do acetaminophen and an NSAID combined relieve osteoarthritis pain better than either alone?

EVIDENCE-BASED ANSWER

Combining nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for short courses provides more relief of pain in osteoarthritis without an increase in side effects (strength of recommendation [SOR]=**B**). Combining acetaminophen at 4 g/d with an NSAID can also decrease the daily dose of NSAID required for pain relief, thus reducing the potential risk from higher-dose NSAID therapy (SOR=**B**).

Over the long term, however, this combination may increase the risk of upper gastrointestinal (GI) bleeding more than that conferred by the NSAID alone (SOR=**B**). If combination therapy is necessary, limiting the dose of acetaminophen to ≤2 g/d minimizes gastrointestinal toxicity. Acetaminophen alone at the lowest dose to provide pain relief is the safest pharmacologic choice for patients with osteoarthritis.

EVIDENCE SUMMARY

Clinical guidelines for osteoarthritis recommend acetaminophen as first-line therapy followed by an NSAID or cyclooxygenase-2 (COX-2) inhibitor, and many patients are treated with combination therapy.

Several small randomized controlled trials have compared the individual efficacy of NSAIDs and acetaminophen in osteoarthritis and have found that both provide more pain relief than placebo.[1–3] There is a trend toward improved pain relief with NSAIDs compared with acetaminophen in the initial treatment period; however, few long-term studies of efficacy have been reported. One randomized controlled trial comparing 750 mg/d naproxen (Aleve, Naprosyn) with 2600 mg/d acetaminophen for 2 years found similar pain relief for both medications and a dropout rate of 65% in both groups.[2] Similar numbers of persons taking acetaminophen or naproxen dropped out because of adverse effects (20%) or lack of efficacy (19%), and no difference was seen in functional improvement between the 2 groups.

A 6-week randomized double-blind crossover trial of 227 patients comparing 75 mg diclofenac and 200 mg misoprostol (Arthrotec) with acetaminophen 4 g/d found the diclofenac-misoprostol combination provided more pain control than acetaminophen alone. Adverse events were slightly more common in the diclofenac group (54% vs 46%; P=.046).[4]

The COX-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex) have been shown to provide equal pain relief compared with naproxen for patients with osteoarthritis.[5] One industry-sponsored randomized trial found rofecoxib superior to celecoxib, and both superior to acetaminophen in treatment of osteoarthritis pain.[6] There was no difference in the incidence of side effects among the 3 medications. Thirty percent of patients taking 4 g/d acetaminophen discontinued the study because of lack of efficacy, compared with 20% of those taking either celecoxib or rofecoxib.[6]

Few studies have evaluated the safety or efficacy of the combination of NSAIDs and acetaminophen in osteoarthritis. One double-blind, double-dummy crossover trial of 18 patients with osteoarthritis of the hip compared naproxen at doses of 500 mg and 1000 mg, with and without 4 g/d of acetaminophen, and 1500 mg/d of naproxen alone over 5 one-week trial periods.[7] Adding acetaminophen improved patient-reported pain scores compared with naproxen alone. Higher doses of naproxen alone provided less pain relief than a lower dose of naproxen combined with acetaminophen. GI side effects increased with the increase in naproxen dose, but were unaffected by the addition of acetaminophen. Functional ability was not affected during this short study. A similar study by the same researchers of patients with rheumatoid arthritis found similar results.[7]

One randomized, double-blind, crossover trial compared single doses of tolmetin (Tolectin, 100,

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150, 200 mg) and acetaminophen (400 mg) alone and in combination with placebo in the control of experimentally induced pain (thermal and electrical stimulation). Acetaminophen alone did not differ from placebo in pain control; however, the combinations of acetaminophen with tolmetin provided similar pain relief to higher doses of tolmetin alone.[8] No studies have evaluated the efficacy or safety of acetaminophen combined with rofecoxib or celecoxib.

Regarding the risks of combining acetaminophen with NSAIDs, 1 nested case-control study based on the entire enrollment panel of the British National Health Service characterized the risk of upper GI side effects among persons taking NSAIDs or acetaminophen alone or in combination. The study evaluated medications in use at the time of an upper GI bleed, controlling for age, sex, and concomitant medications (corticosteroids, H_2 receptor antagonists, omeprazole, anticoagulants, and others) and excluding patients with varices, alcohol-related disorders, liver disease, and cancer; no attempt was made to control other comorbidities. The relative risk of upper GI perforation or bleeding for patients taking ≥2g/d acetaminophen or high-dose NSAIDs was 2.4 (95% confidence interval [CI], 1.7–3.5) and 3.6 (95% CI, 2.9–4.3), respectively. Concomitant use of an NSAID with ≥2 g/d of acetaminophen showed a relative risk of upper GI perforation or bleed of 16.6 (95% CI, 11.0–24.9). Acetaminophen doses <2 g/d conferred no additional risk for serious upper GI side effects.[9]

A systematic review of selective COX-2 inhibitors vs naproxen found fewer endoscopically detected ulcers in patients taking celecoxib but no difference in serious gastrointestinal bleeds.[5] A meta-analysis of randomized controlled trials found a higher incidence of serious thrombotic cardiovascular events among patients taking COX-2 inhibitors compared with naprosyn.[10] The safety profile of rofecoxib and celecoxib in the long-term treatment of pain is not fully understood at this time.

RECOMMENDATIONS FROM OTHERS

The American College of Rheumatology (ACR) recommends acetaminophen up to 4 g/d as a first-line pharmacologic treatment for osteoarthritis of the hip and knee, and advises NSAIDs be used at the lowest effective dose if they are necessary for pain control.[11] The ACR does not specifically comment on combining NSAID and acetaminophen use.

The American Academy of Orthopaedic Surgeons recommends initial use of an NSAID or acetaminophen, but does not comment on the combination of NSAIDs and acetaminophen.[12]

Jennifer J. Buescher, MD, Susan Meadows, MLS,
Department of Family and Community Medicine, University of Missouri–Columbia

CLINICAL COMMENTARY:

Adding acetaminophen may be more desirable than switching NSAIDs

Compared with NSAIDs, acetaminophen has a complementary analgesic mechanism of action and can be safely used in many patients. Additive effects of acetaminophen have not been well described with all NSAIDs (eg, COX-2 inhibitors); however, this combination is inexpensive and overall appears to effectively augment analgesia when combined with NSAIDs. Although observational data demonstrate an increased risk of upper GI bleeding with this combination, selection bias (higher-risk patients being on combination therapy) could reasonably explain this association. Adding acetaminophen may be more desirable than switching NSAIDs for patients with osteoarthritis that have a partial response to their current NSAID therapy.

Joseph Saseen, PharmD, FCCP, BCPS, *University of Colorado Health Sciences Center, Denver*

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DRUG BRAND NAMES

Amoxicillin • Amoxil, Biomox, Polymox, Trimox, Wymox
Cephalexin • Biocef, Keflex
Celecoxib • Celebrex
Diclofenac/Misoprostol • Arthrotec
Ipratropium • Atrovent
Labetalol • Trandate
Methyldopa • Aldomet
Naproxen • Aleve, Anaprox, Naprosyn
Nitrofurantoin • Furadantin, Macrobid, Macrodantin
Rofecoxib • Vioxx
Tiotropium • Spiriva
Tolmetin • Tolectin
Triamcinalone • Aristocort, Atolone, Kenacort
Sulfamethoxazole/Trimethoprim • Bactrim, Cotrim, Septra, Sulfatrim
Sulfisoxazole • Gantrisin