The Impact of NSAIDs and COX-2 Inhibitors on Blood Pressure Control

Sowers JR, White WB, Pitt B, et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Arch Intern Med 2005;165:161–8.

Study Overview

Objective. To evaluate the effects of celecoxib, rofecoxib, and naproxen on 24-hour blood pressure in patients with type 2 diabetes, hypertension, and osteoarthritis.

Design. Multicenter, international, double-blind, randomized trial.

Setting and participants. Patients from 65 centers were eligible for study enrollment if they had osteoarthritis of the hip or knee requiring daily nonsteroidal anti-inflammatory drugs (NSAIDs), type 2 diabetes mellitus requiring an oral hypoglycemic and/or insulin, a glycosylated hemoglobin level < 9%, hypertension being treated with a stable antihypertensive regimen including either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a seated systolic blood pressure ≤ 150 mm Hg. Patients were excluded if they had type 1 diabetes, rheumatoid arthritis, serum creatinine concentration > 1.5 mg/dL, serum potassium concentration > 5.4 mmol/L, or use of any medication that may affect blood pressure, weight, or edema (eg, corticosteroids).

Intervention. Patients were randomly allocated to treatment with celecoxib 200 mg once daily, rofecoxib 25 mg once daily, or naproxen 500 mg twice daily for 12 weeks. All patients were treated with 1000 mg acetaminophen 3 times daily 7 to 10 days prior to study initiation to control osteoarthritic symptoms.

Main outcome measures. The primary outcome was 24-hour ambulatory blood pressure monitoring conducted at randomization and at weeks 6 and 12 of treatment. Blood pressure was measured every 20 minutes throughout the 24-hour ambulatory monitoring period. Secondary outcomes were osteoarthritis signs and symptoms (eg, pain, stiffness) measured using 3 validated arthritis symptom scales.

Main results. 404 patients were randomized, with 136 patients in the celecoxib arm, 138 in the rofecoxib arm, and 130 in the naproxen arm. Baseline characteristics were similar in all treatment groups. 323 (81.6%) patients completed 6 weeks of the trial. The mean ± SE 24-hour systolic blood pressure after 6 weeks of treatment was increased significantly by rofecoxib (from 130.3 ± 1.2 to 134.5 ± 1.4 mm Hg; $P < 0.001$) but not by celecoxib (132.0 ± 1.3 to 131.9 ± 1.3 mm Hg; $P = 0.54$) or naproxen (133.7 ± 1.5 to 133.0 ± 1.4 mm Hg; $P = 0.74$). Similar blood pressure effects were also measured at 12 weeks. 30% of patients with controlled hypertension at baseline developed ambulatory hypertension by week 6 in the rofecoxib arm as compared with 16% in the celecoxib arm ($P = 0.05$) and 19% in the naproxen arm ($P = 0.16$). For the secondary outcomes, all 3 treatments produced significant improvements in osteoarthritis symptoms from baseline at 6 and 12 weeks; there was no significant difference between treatment arms.

Conclusion. Treatment with rofecoxib induced a significant increase in 24-hour systolic blood pressure; this was not seen in the celecoxib or naproxen treatment arms. All 3 treatment arms had some degree of blood pressure destabilization.

Commentary

Meta-analysis of short-term clinical trial data has suggested that NSAID therapy could raise mean arterial pressure from 5 to 10 mm Hg [1,2]. Because blood pressure is correlated to cardiovascular events, increases in blood pressure associated with NSAID therapy may have important public health implications [3]. Clinical trials have demonstrated that NSAIDs may diminish the overall efficacy of certain antihypertensive medications. This effect seems most convincingly demonstrated with diuretics, β blockers, and angiotensin-converting enzyme inhibitors [4–6].

Sowers et al's well-designed randomized trial has convincingly supported earlier findings that NSAIDs may destabilize ambulatory blood pressure. In addition, this study offers several additional insights not evaluated from earlier work. First, the duration of the overall trial was 12 weeks,

which is substantially longer than earlier trials. Second, the study also assessed osteoarthritis symptoms outcomes. This is an important addition because it demonstrated that the increased risk of blood pressure destabilization is not associated with improvement in osteoarthritis symptoms. Finally, the choice of study population (ie, hypertensive diabetics) was salient, as poor blood pressure control in this population is strongly associated with adverse outcomes.

Patients allocated to rofecoxib had the greatest increase in ambulatory blood pressure. Because rofecoxib has been voluntarily withdrawn from the market, this is less of a concern to providers; however, in both the celecoxib and naproxen arms, patients had clinically significant rates of blood pressure destabilization. Future research is needed to determine if these changes in blood pressure are associated with poorer cardiovascular outcomes and if specific NSAIDs are less prone to result in blood pressure changes. In the meantime, providers prescribing NSAIDs and cyclooxygenase-2 (COX-2) inhibitors for daily use should remember to carefully monitor their patients' blood pressure.

Applications for Clinical Practice

Although destabilization was more common in the rofecoxib arm, patients in all 3 treatment arms experienced increased rates of blood pressure destabilization while being treated with NSAID or COX-2 therapy. Clinicians need to carefully monitor their diabetic hypertensive patients who require daily NSAID or COX-2 therapy for blood pressure control.

–Review by Harvey J. Murff, MD, MPH

References

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