COX-2 Inhibitors and the Risk for Hypertension


Study Overview

Objective. To compare the effects of cyclooxygenase-2 (COX-2) inhibitors with placebo, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and each other on blood pressure (BP) elevation and hypertension.

Design. Meta-analysis.

Setting and participants. 19 randomized controlled trials involving COX-2 inhibitors were published before May 2004, with a total of 45,451 participants in which BP data were available. Pooled results of trials involving (1) COX-2 inhibitor exposure versus placebo, (2) COX-2 inhibitor exposure versus NSAID, or (3) rofecoxib exposure versus celecoxib were analyzed. Studies involving fewer than 50 patients or involving treatment of less than 4 weeks’ duration were excluded.

Main outcome measures. Weighted mean difference point-estimate increase in systolic and diastolic BP and the relative risk (RR) of developing hypertension.

Main results. Among the 19 trials, COX-2 inhibitors caused a weighted mean difference point-estimate increase in systolic and diastolic BP compared with placebo (3.85/1.06 mm Hg) and nonselective NSAIDs (2.83/1.34 mm Hg). COX-2 inhibitors were associated with a nonsignificantly higher RR of causing hypertension compared with placebo (RR, 1.61 [95% confidence interval (CI), 0.91–2.84]; P = 0.10) and nonselective NSAIDs (RR, 1.25 [95% CI, 0.87–1.78]; P = 0.23). Rofecoxib induced a point-estimate increase in systolic BP (2.83 mm Hg) and a nonsignificantly higher risk of developing systolic BP elevation (RR, 1.50 [95% CI, 1.00–2.26]; P = 0.05) compared with celecoxib.

Conclusion. COX-2 inhibitors were associated with a point-estimate BP elevation compared with placebo and nonselective NSAIDs. There was a nonsignificantly higher incidence of developing hypertension compared with nonselective NSAIDs.

Commentary

All NSAIDs, including COX-2 inhibitors, have ceiling effects for analgesia. Strong evidence exists for dose-related hypertension, edema, renal dysfunction, and serious cardiovascular events, including myocardial infarction and heart failure, with COX-2 inhibitor use [1–4]. Available data on the potential association of COX-2 inhibitors with hypertension are conflicting because they are drawn from heterogeneous studies not specifically designed to address this issue. Therefore, Aw et al pooled the results of 19 similar trials to determine the magnitude of the risk for developing hypertension when exposed to a COX-2 inhibitor and to see if this risk differed by the type of COX-2 inhibitor used. They also attempted to determine if there was an increased risk of developing hypertension for COX-2 inhibitor users compared with traditional NSAID users.

A meta-analysis is a technique that is used to pool the results of multiple studies. By combining the samples of individual studies, a meta-analysis can greatly increase the overall sample size, power, and precision of the estimate of treatment effects. The quality of the meta-analysis depends heavily upon the quality of the underlying studies, publication bias, and even the search strategy that was used to identify the trials. One of the major limitations of the study by Aw et al was that in the underlying studies, hypertension and in fact BP readings may have been defined in different ways. Two of the studies used 24-hour ambulatory BPs, while others used clinic or office readings. Another limitation of the meta-analysis was the potential heterogeneity of the subjects. The proportion of patients with preexisting hypertension at baseline was noted in only 5 of the 19 studies analyzed. Therefore, it is difficult to determine if the BP increases that occurred with exposure to the drug were in patients with preexisting hypertension or normotensive subjects, and there may have been an underestimate of the study’s findings.

Applications for Clinical Practice

The U.S. Food and Drug Administration has decided that all COX-2 inhibitors carry serious risks of heart attack and
stroke and recommend that these drugs carry black box warnings. Providers and patients should use these drugs cautiously and infrequently given the seriousness of side effects.

—Review by Christianne L. Roumie, MD, MPH

References