Hypertension Associated With Therapies to Treat Arthritis and Pain

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Cyclooxygenase-2 (COX-2) inhibitors have become a widely used class of agents for the treatment of arthritis and pain because of their improved gastrointestinal safety and tolerability profile compared with the nonselective NSAIDs.\(^1,2\) During the past 4 years, the effects of these agents on destabilization of blood pressure (BP) has become a concern that has led to substantial research and controversy. COX inhibition is associated with antinatriuretic and vasoconstrictor effects mediated through the inhibition of the actions of prostaglandin E\(_2\) and prostacyclin.\(^3,4\) The first 2 studies that evaluated the effects of NSAIDs on BP\(^5,6\) demonstrated that mean arterial pressure could rise by as much as 5 to 6 mm Hg in a population of patients with hypertension. The greatest effects of NSAIDs on BP control were observed in patients on monotherapeutic regimens of \(\beta\)-adrenergic blocking drugs, diuretics, or angiotensin-converting enzyme (ACE) inhibitors.\(^6\)

Recent clinical trials suggest that patients treated with \(\beta\)-blockers and ACE inhibitors are particularly susceptible to destabilization of BP control by some COX-2 inhibitors compared with patients controlled with a calcium antagonist.\(^8\) For example, in patients on an ACE inhibitor monotherapy regimen, rofecoxib (25 mg daily) increased the systolic BP by 5 mm Hg, whereas in patients on a calcium antagonist alone, there was no increase in systolic BP. However, not all COX-2 inhibitors have the same effect on BP. In a drug interaction trial involving 178 patients with hypertension, 24-hour ambulatory BP monitoring showed that celecoxib (200 mg twice daily) had a modest and nonsignificant increase in systolic BP in patients treated with a stable dose of the ACE inhibitor lisinopril.\(^9\)

Additionally, the effects of the COX-2 inhibitors have been evaluated in older, hypertensive patients with osteoarthritis in clinical practice trials in which BP had been controlled at stable doses of antihypertensive therapy for at least 3 months.\(^8,9\) After 6 to 12 weeks of treatment, significantly more patients treated with rofecoxib 25 mg once daily had clinically important elevations in clinic and 24-hour systolic BP compared with patients treated with celecoxib 200 mg daily. Although these studies have shown that the incidence of edema was significantly higher in the rofecoxib-treated patients compared with the celecoxib-treated patients, most of the patients developing uncontrolled hypertension did not develop edema or significant weight gain. Hence, interference with the vasodilatory actions of certain antihypertensive drugs may be a more common cause of destabilization of BP control than enhanced plasma volume associated with the antinatriuretic effects of the COX-2 inhibitors.\(^8,9\)

In prior analyses of clinical trials involving nonhypertensive patients with arthritis, nonselective NSAIDs and COX-2 inhibitors have not appeared to have much effect on the development of hypertension.\(^5,7,11\) However, studies in these normotensive populations have had small sample sizes, so one could not accurately predict the BP interaction effects of NSAIDs and COX-2 inhibitors for patients who were newly treated for arthritis and pain in clinical practice.\(^4\)

In this issue of Hypertension, Solomon et al have provided some important insight into the effects of NSAIDs and COX-2 inhibitor therapy on the development of hypertension using a large retrospective case-control study involving >17,000 elderly patients from 2 pharmacy benefit management plans in New Jersey and Pennsylvania.\(^12\) To be included in the study, patients were required to have no prior diagnosis of hypertension nor the use of any class of antihypertensive therapy (except loop diuretics). There were 3915 individuals (ie, cases) who developed newly diagnosed hypertension and subsequently were prescribed an antihypertensive drug. A key finding in the study is that the absolute incidence of new onset hypertension during the 2- to 3-year period of observation was 21% in patients prescribed celecoxib, 23% in patients prescribed NSAIDs, and 27% in the patients prescribed rofecoxib. The background incidence rate of new onset hypertension was 22% in 15,711 patients not using anti-inflammatory drugs during the observation period. Further, the odds of developing hypertension was 1.3 to 1.6 greater in patients receiving rofecoxib than in patients receiving conventional NSAIDs or celecoxib.

Unlike the results of a similar case-control study\(^13\) that showed a significant impact of dose of rofecoxib and the development of acute myocardial infarction in the Medicare study population, Solomon et al did not find a dose-related increase for the onset of hypertension on rofecoxib. However, this finding may be an artifact of a very small number of patients taking a rofecoxib dose >25 mg daily compared with a large number taking lower doses (≤25 mg/d). In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial that had a
The implications of the findings of the Solomon et al study involve 2 important issues. Physicians clearly prescribe NSAIDs and COX-2 inhibitors to normotensive patients with pain or arthritis or both and do not recognize that the development of hypertension may be attributable to the newly prescribed therapy. Hence, patients may end up on antihypertensive drug therapy unnecessarily. Alternatively, patients who have known hypertension that is acceptably controlled could become destabilized by the introduction of a COX-2 inhibitor. Small increases in systolic BP over time in an older hypertensive population are linked to significant increases in coronary heart disease death rates and stroke. Furthermore, in the treated hypertensive population, small mean differences from baseline measures could have clinically relevant results, as has been observed in the treatment groups in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) study.

Finally, Solomon et al reported that the odds of developing hypertension were significantly greater in patients with a history of heart or renal disease or both and who were treated with rofecoxib compared with other NSAIDs and celecoxib. This finding may in part be because of the inability for patients with renal disease to compensate for the antinatriuretic effects of the COX-2 inhibitor. Unfortunately, no clinical trials have been conducted using the COX-2 inhibitors in patients with moderate renal insufficiency and, therefore, great caution should be taken with using rofecoxib or any NSAID in patients with renal insufficiency or heart failure, even for short periods of time.

References
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