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Scientific Update™

Do the different COX-2 specific inhibitors exert different effects on the cardiovascular system?

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Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed in North America for the treatment of various painful musculoskeletal conditions such as osteoarthritis and rheumatoid arthritis.[1] Aspirin and other NSAIDs such as ibuprofen, diclofenac, naproxen, and indomethacin, have demonstrated anti-inflammatory, antipyretic, analgesic, and antithrombotic properties. Antithrombotic agents are beneficial in the treatment of cardiovascular diseases since thrombus formation and platelets play a key role in the acute manifestations of coronary artery disease.[2] However, NSAIDs exert additional pharmacological effects that may have a negative impact on the cardiovascular system. For instance, NSAIDs may attenuate blood pressure control and they are potentially nephrotoxic, especially in elderly patients treated with antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics.[3,4] Meta-analyses of clinical trials conducted to evaluate the effect of conventional NSAIDs in patients treated for hypertension have indicated that NSAIDs induce an average increase of 3.3-5.4 mm Hg in mean arterial blood pressure.[5,6] This destabilization of blood pressure control may be due in part to a reduction in the synthesis of vasodilatory prostaglandins since conventional NSAIDs inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes.[1] Much basic and clinical research has been devoted to the development of specific inhibitors of the COX-2 isoform. COX-2 specific inhibitors such as celecoxib and rofecoxib have been shown to possess anti-inflammatory properties without the adverse gastrointestinal effects usually associated with NSAIDs.[7]

The effects of COX-2 specific inhibitors on the cardiovascular system

Thrombotic risk

The manifestations of the anti-inflammatory and anti-thrombotic effects of COX-2 specific inhibitors on the cardiovascular system include their impact on blood pressure, acute myocardial infarction (MI), and cerebrovascular (CV) events. Clinical studies have been undertaken to compare the anti-inflammatory therapeutic profile of the COX-2 specific inhibitors, celecoxib and rofecoxib, to conventional NSAIDs. Some of these trials have also allowed the investigators to determine the potential cardiovascular effects of selective COX-2 specific inhibitors. For example, the CLASS (Celecoxib Long-term Arthritis Safety Study) trial and the VIGOR (Vioxx Investigation of Gastrointestinal Outcomes in Rheumatoid Arthritis) trial have been conducted to evaluate the therapeutic potential of celecoxib and rofecoxib, respectively.[7,8,9]

In the CLASS trial, cardiovascular adverse event rates were compared between celecoxib 400 mg twice daily (n=3,987) and the NSAIDs diclofenac 75 mg twice daily (n=1,996) and ibuprofen 800 mg three times daily (n=1,985). In the VIGOR trial, the incidence of thrombotic events was compared between rofecoxib 50 mg daily (n=4,000) and naproxen 500 mg twice daily (n=4,000). The MI and CV event rates for the two drugs were evaluated. The celecoxib clinical trial database available before FDA approval of the drug was combined with the results from the CLASS trial. This provided over 8,000 person years of exposure to celecoxib and approximately 3,000 person years of conventional NSAID exposure. Figure 1 illustrates that there was no difference in cardiovascular and cerebrovascular event rates between celecoxib and NSAIDs, and that neither celecoxib, nor the NSAIDs was associated with higher event rates than those observed with placebo.

In the VIGOR trial, an increase in the rate of MI was observed among patients treated with rofecoxib compared to

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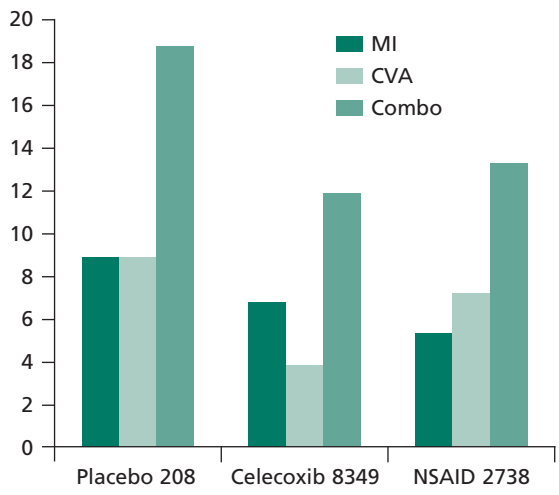
Figure 1: CV thrombotic event rates per 1,000 PY (Pooled RCTs, open label extension, CLASS-AII patients-ASA and non-ASA)



those who received naproxen (0.4% vs. 0.1%, respectively).[8,15] However, the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.[15]

From these analyses, it was hypothesized that differences in the fluid retention and blood pressure effects of celecoxib and rofecoxib might have contributed to the differences that were observed. Differential effects on platelets have not been demonstrated for celecoxib and rofecoxib, and thus are unlikely to account for the differences. Confounding by differential usage of low-dose aspirin and different distributions of cardiovascular risk factors could also have contributed to the differences observed between the drugs.

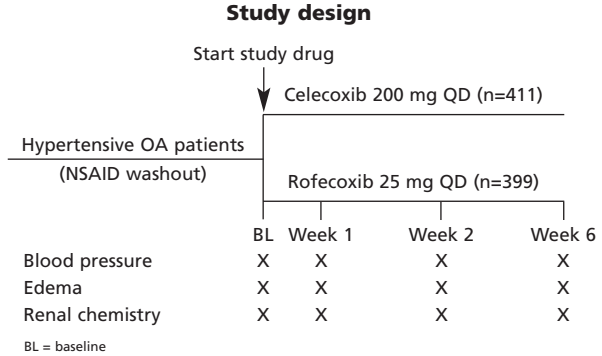
Hypertension/edema/renal function

Studies with celecoxib and rofecoxib indicate that important differences may exist in the incidence of hypertension and peripheral edema associated with the administration of these two COX-2 specific inhibitors. The average incidence of peripheral edema observed with celecoxib is low (2%) and independent of dosage (low dose or supratherapeutic dosing of celecoxib).[9] There was also no evidence of a dose-related increase in hypertension with this agent. In contrast, the administration of rofecoxib (12.5-50 mg daily) was associated with dose-related increases in peripheral edema (3.6, 3.8 and 6.3% for the 12.5, 25 and 50 mg doses, respectively), and hypertension.[9]

The OA/HTN trial

This multicenter, randomized, double-blind, parallel group study was designed to compare the incidence of clinically significant cardiovascular and renal adverse events associated with the most commonly prescribed therapeutic doses of celecoxib (200 mg once daily) and rofecoxib (25 mg once daily).[9] The OA/HTN study (Figure 2) was conducted for 6 weeks and included elderly

Figure 2: 6-Week OA/HTN Trial: Celecoxib vs Rofecoxib



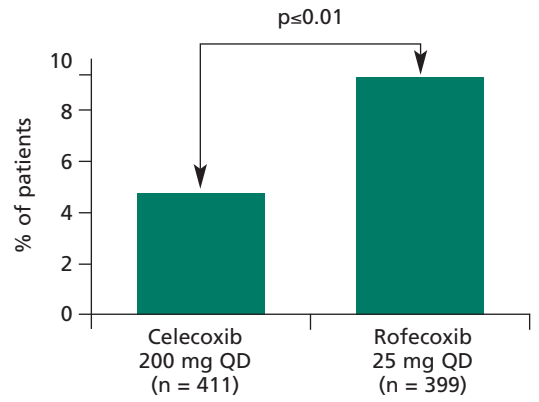
hypertensive patients (≥65 years; mean = 74) with osteoarthritis (celecoxib n=411; rofecoxib n=399). Osteoarthritis (OA) and hypertension (HTN) are both common diseases in the elderly.

All patients were being treated with antihypertensive medication and received a stable dose of their antihypertensive therapy (ACE inhibitors, beta-blockers, diuretics, calcium channel blockers, or combination therapy) for at least 3 months prior to study entry. The mean duration of hypertension was 12-13 years; patients had a history of osteoarthritis of 12-14 years on average. Mean blood pressure was 138/76 mm Hg (celecoxib group) and 137/76 mm Hg (rofecoxib group). Baseline serum creatinine had to be <132 mmol/L (1.5 mg/dL). There were no exclusions for a history of cardiovascular events or edema, or use of aspirin

Pre-defined clinically significant endpoints for blood pressure and for edema were determined for patients at baseline and at weeks 1, 2 and 6. To assess the effect of the drugs on blood pressure, the mean blood pressure change from baseline was calculated. For systolic blood pressure (SBP), changes >20 mm Hg and increases to >140 mm Hg were determined. For diastolic blood pressure (DBP), changes >15 mm Hg and increases to >90 mm Hg were determined. Clinically significant changes in edema were measured on a scale of 0-4+. Measurements of renal function were also performed.

At the end of the study, there was a significantly greater increase in the incidence of peripheral edema in the group of patients treated with rofecoxib (9% vs 5%, $p<0.01$) as illustrated in Figure 3.[9] In addition, nearly 60% more patients on rofecoxib than on celecoxib experienced clinically significant SBP increases ≥20 mm Hg ($p<0.05$).[9] This difference in incidence of clinically meaningful elevations in SBP between rofecoxib and celecoxib reached statistical significance at week 2 of the clinical trial and persisted at week 6 (Figure 4). The mean SBP was also increased significantly from baseline ($p<0.01$) in the rofecoxib versus the celecoxib group at all time points. The observed differences in BP are of particular importance, as increases in SBP represent a powerful independent predictor of cardiovascular disease risk, especially in elderly individuals.[10] For example, with rising SBP there is a higher risk of coronary heart disease mortality. Even modest increases in SBP are associated with a considerably increased risk

Figure 3: 6-Week OA/HTN Trial: Incidence of edema



for adverse cardiovascular outcome (Table 1).[11] This may be due, in part, to the fact that most individuals develop an increase in arterial stiffness during the aging process that particularly affects the aorta and other elastic arteries, leading to an increase in SBP.[10] Systolic hypertension accounts for over 50% of hypertensive cases in the elderly, probably as a result of this arterial stiffening that occurs with aging.[13] The benefit of antihypertensive treatment in decreasing the incidence of stroke, MI and left ventricular failure has been demonstrated to apply to patients with isolated systolic hypertension.[12,13] Large-scale, randomized trials have provided conclusive evidence that reduction in high blood pressure in the elderly can effectively and safely decrease cerebrovascular and cardiovascular morbidity and mortality rates.[13]

The SHEP Study

The Systolic Hypertension in the Elderly Program (SHEP) was the first study to specifically address the ability of antihypertensive drug therapy to reduce the risk of nonfatal and fatal stroke in elderly patients with isolated systolic hypertension.[14] SHEP was a multicenter, randomized, double-blind, placebo-controlled trial

Table 1: Even modest increases in SBP are associated with increased risk of adverse cardiovascular outcome.

BP Group	SBP level	Relative risk
Optimal	<120	1.00 (reference)
Normal	120-129	1.28 (1.19-1.36)
High normal	130-139	1.66 (1.56-1.77)
Stage 1	140-159	2.45 (2.30-2.61)
Stage 2	160-179	3.42 (3.16-3.71)
Stage 3	180-209	5.26 (4.68-5.90)
Stage 4	210+	6.40 (4.74-8.65)

Based on Neaton JD, in Laragh and Brenner editors; *Hypertension,* 1995

that included 4,736 participants with a mean age of 72 years. Participants had SBP ranging from 160 to 219 mm Hg (average SBP:170 mm Hg) and DBP was < 90 mm Hg (average DBP:77 mm Hg). Patients were randomly assigned to one of two treatment groups: placebo (n=2,371) or antihypertensive drug treatment (12.5 mg daily of chlorthalidone (step 1); either 25 mg daily of atenolol or 0.05 mg daily of reserpine (step 2); n=2,365). Hypertensive participants were followed for an average of 4.5 years. Antihypertensive therapy produced a significant reduction in systolic blood pressure. The 5-year average systolic blood pressure was 143 mm Hg for the group of patients treated with antihypertensive drugs and 155 mm Hg for patients who received placebo.[14] Active treatment produced a 36% decrease in the incidence of total stroke. Another noteworthy finding was the striking reduction in the incidence of heart failure (reduced by 55%), and the incidence of myocardial infarction (reduced by 27%.)[14]

The HOT Study

It is well documented from these and other trials that antihypertensive treatment may reduce the risk of cardiovascular morbidity and mortality.[17] The issue of by how much blood pres-

Figure 4a: 6-Week OA/Hypertension Trial: Incidence of systolic blood pressure >20 mm Hg and >140 mm Hg

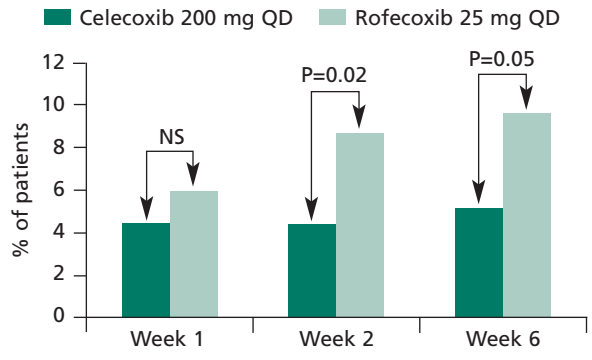
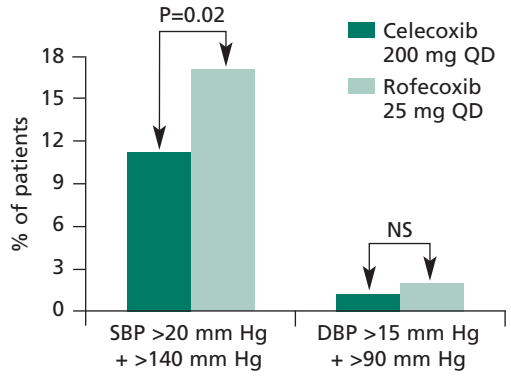


Figure 4b: 6-Week OA/Hypertension Trial: Incidence of clinically important blood pressure elevation



sure should be lowered to obtain the greatest benefit, in terms of reduction in cardiovascular morbidity and mortality, has been a subject of debate. The Hypertension Optimal Treatment (HOT) study was conducted to define the optimal target blood pressure during the treatment of hypertensive patients (ie, the level of blood pressure associated with the lowest incidence of major cardiovascular events such as fatal and non-fatal stroke and myocardial infarction and all other cardiovascular deaths).[17]

The HOT study recruited 18,790 hypertensive patients from 26 countries, with a mean age of 61.5 years, mean DBP 105 mm Hg, and mean SBP 170 mm Hg. Patients were randomized into three groups with different target DBPs: 90 mm Hg (n=6,264), 85 mm Hg (n=6,264), or 80 mm Hg (n=6,262). All patients received antihypertensive therapy with the calcium antagonist felodipine (5 mg q.d.) as a first step, with additional medication added in a step-wise fashion as per a fixed protocol.[17] The investigators found that to prevent major cardiovascular events, the lowest point of risk was obtained at a mean DBP of 82.6 mm Hg and at a mean SBP of 138.5 mm Hg. The lowest risk of cardiovascular mortality was at a DBP of 86.5 mm Hg and an SBP of 138.8 mm Hg. Further reduction in these blood pressure values was safe, but without additional benefit. Thus, the HOT study highlights the fact that even small differences in DBP may be associated with significant differences in event rates.

Other trials

There are other, independent, trials that also suggest that celecoxib and rofecoxib may differ in their effects on BP and renal function compared to conventional NSAIDs. The hypertensive side effects of celecoxib were compared to those induced by the NSAIDs, ibuprofen and diclofenac in the CLASS study. The results of this trial indicated that the incidence of adverse hypertensive events was significantly lower with celecoxib compared to ibuprofen (2.0% vs. 3.1%, respectively). In addition, increases in the concentrations of blood urea nitrogen (BUN) and/or serum creatinine were significantly greater with the NSAID diclofenac (administered at 150 mg daily) than with celecoxib (2.1% vs. 1.2%).

A randomized study was conducted with 75 participants aged 60 to 80 years to determine the effect of rofecoxib on renal function in elderly patients on a low-sodium diet.[16] Rofecoxib was compared to the NSAID indomethacin. The renal parameters measured were: glomerular filtration rate, creatinine clearance, urinary and serum sodium and potassium values. Rofecoxib was found to induce a reduction in the glomerular filtration rate that was comparable to that produced by indomethacin (0.23 mL/s vs. 0.18 mL/s, respectively). Changes in creatinine clearance, urinary and serum sodium and potassium were less pronounced.[16]

Conclusions

- The COX-2 specific inhibitors celecoxib and rofecoxib display potentially different thrombotic risk profiles, as measured by the MI and CV event rates for the two drugs.
- Different clinical trials have revealed no difference in MI and CV rate between celecoxib and NSAIDs, while an increase in the rate of MI was observed for rofecoxib compared to naproxen.
- Important differences appear to exist in the incidence of hypertension and peripheral edema associated with celecoxib versus rofecoxib therapy.
- Compared with celecoxib 200 mg q.d., rofecoxib 25 mg q.d. is associated with a significant increase in:
  - the incidence of peripheral edema
  - mean SBP
  - clinically meaningful SBP elevations
- These clinical investigations suggest that celecoxib has an excellent cardiovascular and renal safety profile, which may help to differentiate this therapeutic agent not only from conventional NSAIDs, but also from other COX-2 specific inhibitors.

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